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THE AETIOLOGY OF CANCER AND ALLIED DISEASES

DEVELOPMENT OF A CONCEPT BASED ON RECENT EXPERIMENTS DEALING WITH A CELL-FREE TRANSMISSION OF MOUSE LEUKAEMIA

BY

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It has long been suspected that cancer and allied diseases may be caused by transmissible viruses. This concept appeared particularly plausible as a hypothetical explanation of the obscure aetiology of various forms of leukaemias, lymphosarcomas, and Hodgkin's disease. The course of either disease in humans with the accompanying fever; the frequent temporary improvements followed by relapses; the general systemic manifestations, including the gradual loss of weight and anaemia; the striking, though rare, reports of familial incidence in humans and in animal hosts, were consistent with the assumption of a chronic infectious nature of these diseases.

The main difficulty, however, in accepting the infectious concept of the aetiology of malignant tumours, including leukaemias, has been the well-established observation that in humans, and in animal hosts, tumours are not transmissible from one host to another, at least not in a manner similar to that observed in other infectious diseases. When speaking of a communicable disease we are conditioned to think automatically of a disease spreading from one host to another within the same generation; by contact (smallpox), through infected food or carriers (typhoid fever), through airborne droplets (common cold, influenza), etc. In each case both the infecting and the infected hosts belong to the same generation; a brief interval of time, most frequently not exceeding a few days, or weeks at the utmost, elapses between the individual cases forming successive links in the chain of a conventional transmission of the common communicable disease.

In the typical cases the human observer can actually follow the spread of a communicable disease, tracing it in either direction, back to the infecting carrier, or ahead to the infected host. Thus, a child suffering from chicken-pox, or measles, for instance, could readily cause a rapidly spreading epidemic, progressing from one child to another in the neighbourhood. Similarly, a mouse infected with the salmonella organism would spread typhoid rapidly to other mice within the same cage. Malignant tumours, including the various forms of leukaemias, are obviously not transmissible in such a manner. A leukaemic or sarcomatous chicken could be placed for the balance of its life in close quarters with a flock of healthy chickens; a leukaemic mouse, or a mouse bearing a large, perhaps even ulcerated mammary carcinoma, could be placed in the same cage with a group of healthy mice; yet no transmission of the disease would occur in either case. A similar observation has been repeatedly made, over the period of decades, in human tumours and leukaemias. It appeared logical to conclude, therefore, that malignant tumours, including leukaemias, are not transmissible diseases.

Thus the viral theories of cancer, advanced now and then during the past decades, appeared to be doomed at the onset, and fell in disrepute when confronted with common observations in clinical medicine and experimental laboratories. Actually, however, upon reviewing clinical and experimental observations thus far accumulated, it does not seem necessary to conclude that cancer and leukaemias are not caused by transmissible agents. It can only be concluded that malignant tumours do not appear to be transmitted from one host to another in the conventional manner hitherto observed in the common communicable diseases.

"Vertical" Transmission of Oncogenic Agents

The transmission of oncogenic agents from one host to another may take place in a different manner, not usually observed in the common infectious diseases. Instead of spreading "horizontally" among hosts of the same generation, a potentially pathogenic agent may instead be transmitted from a carrier host to the host's offspring, thence to the offspring's offspring, thence, in turn, to the next generation, and so forth. Such a transmission would obviously require much more time than that observed in those communicable diseases which spread in the conventional manner within the same generation. The term "vertical transmission" or "vertical epidemic" was suggested (Gross, 1944) to designate the transmission of potentially pathogenic agents from one generation to another, usually through germinal cells, occasionally through mothers' milk, as in the case of mouse mammary carcinoma (Bittner, 1936). The agent, though potentially pathogenic, would remain latent for a long period of time, often perhaps throughout the entire life-span of a given carrier host. During such an interval of time the potentially pathogenic agent would remain frugal and moderate in its requirements, causing no harm to its carrier host. Thus the host would remain in perfect health, while carrying and transmitting the seeds of the disease.

In some of the hosts, however, particularly in those reaching middle age, the agent may become activated. Triggered by intrinsic or extrinsic stimuli, the hitherto latent and harmless agent would then change into a formidable pathogen, causing rapid multiplication of

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cells harbouring it, and killing its carrier. In most instances, however, activation of the agents would not occur. The hosts would remain in good health, even though they would carry the agent and transmit it to their offspring.

The triggering factors responsible for the activation of the hitherto latent agents would be of varied nature, generally non-specific. Essentially, these triggers would be either intrinsic (metabolic or hormonal) or extrinsic (such as *x* rays and other forms of ionizing radiation energy, certain chemical poisons, physical factors such as prolonged irritation, etc.).

Viral Aetiology of Cancer and Leukaemia

On the basis of this working hypothesis, one could regard the development of a malignant tumour or that of leukaemia as the result of an activation, perhaps accidental, of oncogenic agents, hitherto latent, and carried by the host. Fortunately, in most instances no activation of the oncogenic agents would occur during the life-span of the host, even though such agents would be transmitted to the host's offspring. Thus only now and then malignant tumours or leukaemia would develop in some of the members of those families in which the agents would be transmitted from one generation to another. Such instances, however, representing only unhappy "accidents" in the otherwise harmonious relationship between the host and its usually well adjusted and latent oncogenic agents, would often be separated by two or three generations of healthy carrier individuals. In humans, therefore, two cases of leukaemia or other malignant tumours representing successive links in the generation-to-generation transmission of the same oncogenic agent might frequently be separated by a century or two. It is quite obvious that the tracing of the "vertical" host-to-host transmission of oncogenic agents in man would be extremely difficult.

The concept of vertical transmission of oncogenic agents may be new as applied to tumours. Actually, however, there exist in nature numerous examples of pathogenic agents transmitted from one generation to another. A virus disease of the silkworm, pebrine, is transmitted through the eggs from one generation to another (Pasteur, 1865). The mosaic disease of lettuce, tomato, or potatoes is caused by viruses transmitted from one generation to another through the seeds, or in the case of potatoes through the tubers; these viruses may remain latent for long periods of time (Kunkel, 1928). The infected plant may grow next to a healthy one, yet no transmission of the virus will occur among hosts of the same generation, unless an intermediary carrier, such as an insect vector, is interposed. In certain instances the vertically transmitted agents may be so adapted to their own hosts that they will not cause harm to their own carriers but may become pathogenic when transmitted to other breed or species. The Rocky Mountain spotted-fever rickettsiae, or the tularaemia organisms, for instance, are transmitted in the tick, through the eggs of these insects, from one generation to another. They cause no harm to their carrier hosts, but may become pathogenic and cause disease when transferred to other species, such as humans.

The temperate phage may also be transmitted from one generation to another in certain lysogenic bacterial clones (Lwoff, 1953). The phage may remain perfectly harmless to its hosts, as a prophage. In very rare instances it may spontaneously become pathogenic, destroying its own host by lysis. The activation may be prompted at will, however, by certain inducing agents, such as ultra-violet (Lwoff *et al.*, 1950) or *x*-ray irradiation (Latarjet, 1951).

It is obvious that the vertically transmitted pathogenic agents can readily escape detection, since they are submicroscopic, and since they only occasionally cause symptoms of disease.

Transmission of Tumours by Filtrates

It is difficult to determine the nature of an obscure disease with the rather limited means available in an experimental laboratory. One of the first steps consists usually in an attempt to transmit the disease from one host to another.

It should be stressed that there are no particular criteria to indicate, *a priori*, whether a given disease is caused by a transmissible agent. In many instances, when studying a new and obscure disease, the investigator may be confronted with symptoms appearing to develop "spontaneously." Yet the disease may be communicable, even though it may be quite difficult to trace the mode of transmission of the pathogenic agent. If experimental transmission succeeds in the laboratory by means of inoculation of filtrates, it can be assumed that the investigated disease is actually caused by a transmissible filterable agent, presumably of viral nature. It still remains to be determined, however, how the actual transmission of the agent occurs under natural conditions of life (Tables I and II).

TABLE I.—*Transmission of Tumours by Filterable Viruses in Animals*

1898	Rabbit myxomatosis	Sanarelli
1908	Chicken leukaemia (erythromyeloblastosis)	Ellermann and Bang
1911	Chicken sarcoma	Rous
1932	Rabbit fibroma	Shope
1932	Dog oral papilloma	DeMonbreun and Goodpasture
1933	Rabbit papilloma	Shope
1933	Chicken lymphomatosis	Furth and Breedis
1934	Dog lymphosarcoma	DeMonbreun and Goodpasture
1936	Mouse mammary carcinoma	Bittner
1936	Rabbit oral papilloma	Parsons and Kidd
1938	Frog kidney carcinoma	Lucke
1946	Chicken lymphoid tumours and osteopetrosis	Burmester *et al.*
1951	Mouse leukaemia	Gross
1951	Horse cutaneous papilloma	Cook and Olson
1953	Mouse parotid carcinoma	Gross
1955	Mouse sarcoma	Gross
1955	Deer fibroma	Shope
1957	Swiss mouse leukaemia	Friend
1958	Hamster sarcoma	Eddy *et al.*

TABLE II.—*Transmission of Human Tumours from Man to Man by Filtered Extracts*

1907	Warts	Ciuffo
1919	Warts	Wile and Kingery
1917	Condyloma acuminatum*	Waelsch
1923	Laryngeal papilloma	Ullmann

* Extract not filtered.

The discovery by Ellermann and Bang in 1908 that leukaemia in chickens could be transmitted by cell-free extracts provided the first experimental support of the concept of viral nature of leukaemia. Even though the cell-free transmission was accomplished only in the fowl, it strengthened the suspicion that in mammals also leukaemia may be caused by similar filterable agents.

"Spontaneous" Mouse Leukaemia

Leukaemia occurs as a spontaneous disease in various strains of mice. In some strains, such as C3H or C57 Brown, it develops only occasionally. In other strains it is more frequent, and in two outstanding inbred strains of mice—namely, C58 and Ak—leukaemia develops spontaneously in up to 90% of middle-aged animals. Over 25 years ago mice of the strain designated by the symbol C58, and bred by MacDowell and Ritcher (1935), were observed to die with large spleens; it was then realized that mice of this particular strain develop leukaemia spontaneously. On the other hand, Furth and his associates (1933) developed purposely a high leukaemic strain of mice by breeding selectively relatives of leukaemic mice and continuing such selective inbreeding through a number of successive generations; they designated this particular leukaemic strain by the symbol Ak. Leukaemia, usually of the lymphatic type, develops in middle-aged Ak mice of both sexes, though the onset begins slightly earlier in females. The incidence of spontaneous leukaemia in a sample of 500 Ak females was in our laboratory 94% at 8.6 average age (Gross, 1958b). It begins to develop approximately at 4 to 4½ months of

age; this incidence rises rapidly, reaching its peak at 7 to 9 months, then declines gradually.

The development of spontaneous leukaemia in over 85% of middle-aged mice in certain inbred lines of mice, such as C58 or Ak, raised immediately the question whether a virus transmitted from one generation to another in certain families of mice may not be actually responsible for the development of this disease. The existence of a leukaemic agent, though long suspected, was not established, however, until the experimental conditions were recognized under which mouse leukaemia could be transmitted by filtrates. All previous attempts to transmit mouse leukaemia by filtered extracts failed prior to 1951 (Gross, 1958b). Transmission of leukaemia in mice appeared possible only when live cells were transplanted from a leukaemic mouse to another host usually of the same or of a genetically related inbred line.

Transmission of Mouse Leukaemia by Filtrates Inoculated into Newborn Mice

A few years ago it was unexpectedly found in our laboratory (Gross, 1951a) that naturally occurring "spontaneous" mouse leukaemia could be transmitted by filtered extracts, provided that certain experimental conditions were met. Thus, newborn, less than 16 hours old, mice of a low leukaemic but susceptible inbred strain—namely, the C3H inbred line (with an incidence of spontaneous leukaemia less than 0.5%)—could be successfully inoculated with filtered extracts prepared from spontaneous Ak leukaemia.

Leukaemia developing in C3H mice following inoculation of the leukaemic filtrates was usually of the lymphatic type, and resembled essentially that which develops spontaneously in mice of the Ak strain. Of a total of 328 newborn C3H mice inoculated with filtrates, 28% developed leukaemia at an average age of 10 months. This compared with an incidence of less than 1% among 166 littermate controls (sister and brothers), either not treated or inoculated simultaneously with heated (65° to 68° C. for half an hour) leukaemic extracts, and surviving to an average of 16 months (Gross, 1951–8).

Surprisingly, among the inoculated C3H mice, some developed, instead of leukaemia, bilateral parotid gland carcinomas, and a few developed subcutaneous fibrosarcomas (Gross, 1953). These results were later confirmed and extended by Woolley and Small (1956), Furth *et al.* (1956), Rudali *et al.* (1956), Dulaney *et al.* (1957), Hays *et al.* (1957), and Kassel and Rottino (1958).

One of the initial difficulties in transmitting mouse leukaemia by filtrates was due to the difference in susceptibility among the strains used for inoculation of the extracts (Gross, 1955); furthermore, it soon became evident that the results of individual experiments may vary to a considerable degree, depending on the extract used. Of 70 leukaemic filtrates, each prepared from a different donor, and tested in our laboratory, 18 were found to be completely inactive on inoculation tests (Gross, 1957b).

Selecting a particularly potent extract, and passing the agent serially through several successive inoculations of newborn hosts, made it recently possible to develop a very potent filterable mouse leukaemia strain (Gross, 1957a). Filtrates prepared from this passage virus can now be inoculated into suckling C3H mice 1 to 14 days old, inducing leukaemia in up to 97% of the inoculated mice after a latency of only three to four months (Gross, 1958a).

It is quite interesting that leukaemic filtrates inoculated into C3H mice less than 16 hours old induce leukaemia, and in some instances parotid gland tumours, whereas the same filtrates inoculated into suckling C3H mice 1 to 14 days old induce leukaemia but not parotid tumours (Gross, 1958a). It appears, therefore, that in order to induce parotid tumours, newborn, less than 16-hours-old, C3H mice have to be inoculated with the leukaemic extracts.

Previous attempts to transmit Ak leukaemia by inoculation of filtrates into adult C3H mice were seldom successful. After the potency of the leukaemic agent has been increased through serial cell-free passage, it is now possible, however, to induce leukaemia also by inoculating passage leukaemic filtrates into adult C3H mice; the incidence of induced leukaemia is approximately 37% after a latency of seven months (Gross, 1958a). Suckling, 1 to 14-days-old, C3H mice, however, are substantially more susceptible to the inoculation of the leukaemic filtrates than adult hosts.

It is apparent, therefore, that the induction of different types of tumours requires the use of a suitable recipient strain for inoculation of the leukaemic extracts. Moreover, the cell-free extracts must be inoculated into newborn mice less than 16 hours old, if the full array of the different types of tumours is to be induced.

The development of leukaemia in some of the mice inoculated with the filtrates, and that of parotid carcinomas or subcutaneous fibromyxosarcomas in others, raised immediately the fundamental question whether a single agent may be able to cause different types of tumours, or whether several distinct agents were present in the leukaemic extracts.

One could assume that one agent may be able to induce different types of tumours. It is also possible to speculate, however, that certain tumours, at least, may carry, either accidentally or for a good reason, a number of distinct oncogenic agents. Under proper experimental conditions some of these hitherto latent agents may assert themselves, inducing a wide spectrum of different tumours. Such a hypothesis would explain the puzzling results of experiments reported by Graffi *et al.* (1956) and Friend (1957).

Development of Leukaemia Following Inoculation of Newborn Mice with Cell-free Extracts from Transplanted Mouse Tumours

The use of newborn, less than 1 day old, mice for inoculation of oncogenic agents, so successful in studies on cell-free transmission of mouse leukaemia (Gross, 1951–3), soon became a useful tool, and proved a source of unexpected findings also in other laboratories.

Thus, Graffi and his co-workers prepared filtered extracts from Ehrlich ascites mouse carcinoma, and from several other mouse tumours. These extracts were then inoculated into newborn mice of a low leukaemic inbred strain (designated by the symbol Agnes-Bluhm and having an incidence of spontaneous leukaemia less than 1%); newborn non-inbred mice designated by symbols M and W were also injected. As a result, 34% to 75% of the inoculated mice developed a myelogenous form of leukaemia, after an average latency varying from 113 to 224 days. The most potent extracts were those prepared from Ehrlich carcinoma and from three closely related mouse sarcomas. Of 332 control mice inoculated with either normal organ extracts from mice, rats, chickens, or rabbits, or with rat-tumour filtrates, less than 1% developed leukaemia (Graffi *et al.*, 1956).

Friend inoculated cell-free centrifuged extracts from Ehrlich ascites carcinoma into newborn Swiss mice. After a latency of 14 months, some of the inoculated mice developed a form of myelogenous leukaemia. This leukaemia was found to be transmissible by intraperitoneal inoculation of filtrates into young adult Swiss mice, inducing leukaemia after only several weeks (Friend, 1957).

It is quite possible, therefore, that there exist different forms of mouse leukaemia, caused by distinct though probably related viruses, requiring different experimental conditions for cell-free transmission. Certain leukaemic agents may require newborn hosts for transmission; others may also infect adult hosts of a suitable line. In this respect, mouse leukaemia would not be different from the various forms of chicken leucosis (Furth *et al.*, 1933; Burmester *et al.*, 1946; Beard, 1957).

Electron Microscopical Studies of the Mouse Leukaemia Agent

Electron microscopical examination of the leukaemic filtrates in drop preparations, shadowed with chromium,

revealed the presence of spherical particles, varying in average diameter between 60 and 70 mμ (Gross, 1956).

More detailed studies were possible on thin sections of the leukaemic tissues. In collaboration with L. Dmochowski, sections were prepared from thymus, cervical glands, and livers from C3H mice in which leukaemia was induced by inoculation of the leukaemic filtrates. Characteristic spherical virus-like particles, most of them averaging approximately 100 mμ, and showing dense centres, were found in large numbers in the cytoplasm and in extracellular spaces (Dmochowski and Grey, 1957). Examination of normal mouse tissues did not reveal the presence of similar virus-like particles; additional studies are necessary, however, to clarify this point further. It is possible that the particles visualized in drop preparations represent the dense centres of the large particles observed on the sections. Technical differences in the manner of preparing the drop preparations as compared with ultra-thin sections may also account for the difference in size of the particles.

Multiplication of the Parotid Tumour Agent in Tissue Culture

In a series of experiments Stewart and her associates (1957) at the National Cancer Institute succeeded in demonstrating the survival and possibly also multiplication of mouse-leukaemia-derived parotid tumour agent in tissue culture media. After passing the agent through monkey kidney, or chicken chorion allantoic membrane culture media, inoculation into newborn, less than 12 hours old, (C3Hf × AKR) F_1 hybrid mice induced in up to 51% of the mice the development of parotid tumours and other neoplasms after a latency varying from 2½ to 10 months. Control mice injected with fluids from uninoculated tissue cultures failed to develop tumours. More recently Eddy and her associates (1958) at the National Cancer Institute made the remarkable observation that the mouse-leukaemia-derived agent passed through tissue culture media induced multiple malignant tumours, most frequently sarcomas, following inoculation into young, less than 4 weeks old, Syrian hamsters.

Attempt to Transmit Radiation-induced Leukaemia by Filtrates

One of the greatest difficulties in the proper interpretation of results obtained with experimental transmission of tumours and leukaemia by means of filtrates has been the fact that in many instances morphologically similar tumours could be obtained with chemical carcinogens, hormones, or ionizing radiation.

The fact that ionizing radiation, hormones, or carcinogenic chemicals may be able to induce tumours and/or leukaemia does not necessarily imply, however, that these tumour-inducing factors are similar in their pathogenic action to oncogenic viruses.

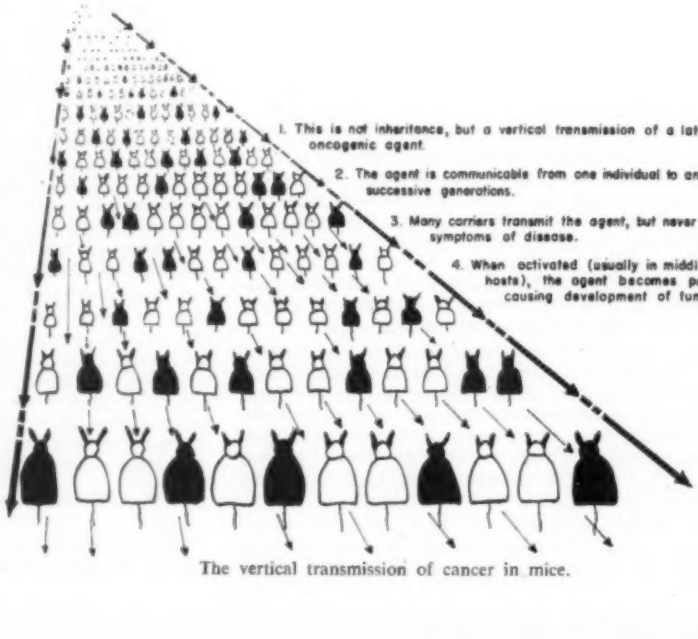
Theoretically, at least, it may be possible to assume that carcinogenic chemicals, hormones, or ionizing radiation may induce leukaemia in mice indirectly only, by activating latent viruses carried in an inactive form by apparently healthy hosts.

In order to determine whether radiation-induced leukaemia could be transmitted by filtrates, the following experiment was carried out (Gross, 1958c).

Leukaemia was induced in mice of a low-leukaemic strain (C3H) by fractionated total-body *x*-ray irradiation (150 r once a week for four to six consecutive weeks). Up to 50% of the irradiated mice developed leukaemia after seven to nine months. An attempt was then made to recover from such mice an oncogenic agent; filtered extracts were prepared from livers, spleens, and thymic lymphosarcomas from the leukaemic donors; the filtrates so prepared were then inoculated into newborn C3H mice. Of 148 inoculated mice, 16 (11%) developed leukaemia after approximately one year, and 7 (5%) developed parotid gland tumours (Gross, 1958c). Similar results have been recently obtained by Kaplan (1958) on C57 Black mice. These experimental findings suggest that mice of a low leukaemic strain may carry a latent leukaemogenic agent of a low pathogenic potential. When triggered by repeated total-body *x*-ray irradiation such an agent may become pathogenic, and induce leukaemia in its hosts. Once activated, this agent may then, at least in some instances, be separated from cells by filtration, and transmitted by inoculation into newborn hosts of a susceptible strain.

There may exist a large variety of tumours which, although similar in their morphology, may be individually distinct. It is entirely possible that ionizing radiation, hormones, or chemical carcinogens merely activate latent oncogenic viruses; their tumour-inducing action could thus be compared to the experimental induction of bacteriophages in lysogenic bacteria (Lwoff, 1953). Accordingly, oncogenic viruses could be compared to temperate bacteriophages, transmitted from one generation to another in lysogenic bacterial hosts, only very occasionally killing their carriers (Gross, 1954; Latarjet, 1954).

Should this hypothesis prove to be correct, it would then logically follow that individuals with symptoms of tumours or leukaemia would represent only a small fraction of those actually carrying the seeds of either disease. This concept would also explain the striking though not too frequent cases of familial occurrence of tumours and leukaemia not only in animals but also in humans. Although in most instances cancer or leukaemia occurs in man only sporadically, yet numerous instances, some of them striking, have been recorded in which malignant tumours and/or leukaemia developed in two or more members of the same family, either within the same or in successive generations. Cases of either tumours or leukaemia developing in brothers, brothers and sisters, or in a child and in one of its parents, grandparents, aunts, uncles, or cousins, have been recorded by numerous observers. One of the most striking families


1. This is not inheritance, but a vertical transmission of a latent oncogenic agent.
2. The agent is communicable from one individual to another of successive generations.
3. Many carriers transmit the agent, but never show any symptoms of disease.
4. When activated (usually in middle aged hosts), the agent becomes pathogenic, causing development of tumors.

The vertical transmission of cancer in mice.

has been reported by Anderson (1951): five out of eight siblings developed leukaemia when 5 to 8 years old.

Vertical transmission of potentially pathogenic agents should not be confused with inheritance. The differentiation is not always easy. When observing a disease appearing in several descendants of successive generations within the same family of hosts, a casual observer may consider such cases to be caused by some obscure inherited genetic factors. Yet inheritance is conditioned by genetic factors, transmitted in an orderly and foreseeable manner, and is not acquired. Vertically transmitted diseases, on the other hand, are caused by viral agents, and represent a form of infection. The potentially pathogenic agents had been most probably at one time acquired, even if this might have happened in individual families many thousands of years ago; transmitted, since that time, from one generation of their hosts to another, invisible and completely adapted, such agents represent examples of "perfect parasites," causing in most instances no harm to their hosts. Only now and then, prompted by obscure reasons, they may change into formidable pathogens, causing symptoms of fatal disease and destroying their hosts. Such "accidents," however, would be usually separated by several generations of apparently healthy carrier-hosts.

It is quite possible that not only in animal species but also in humans malignant tumours, including the various forms of leukaemias, are caused by oncogenic agents seeded in millions of apparently healthy hosts and transmitted from one generation to another (Gross, 1954).

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EFFECT OF INSULIN AND GLUCAGON ON TUMOUR GROWTH

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During the past few years we have been working on certain problems related to both insulin and glucagon (Salter and Best, 1953; Salter *et al.*, 1957a, 1957b; Davidson *et al.*, 1957). There is considerable evidence in the earlier literature that insulin may cause some inhibition in the growth of malignant tissue (Piccaluga and Cioffari, 1925; von Witzleben, 1925; Silberstein *et al.*, 1927; Gomes da Costa, 1931).† The results of experiments carried out in this laboratory are in general agreement with these earlier reports. We find that, although the effects of giving insulin to rats bearing the Walker carcino-sarcoma vary considerably, a small but significant inhibition of the growth of this tumour is produced in most instances. The findings presented in this preliminary communication show, for the first time, that glucagon alone also produces a significant inhibition in the growth of this tumour, while the simultaneous treatment with both glucagon and insulin consistently causes an inhibition that is considerably greater than the sum of their individual effects.

Methods

Female Wistar rats weighing approximately 150 g. were used in all experiments. The animals were fed powdered Purina chow containing 5% corn oil.

Walker carcino-sarcoma tissue was collected from several donor rats, pooled and macerated with three parts (by weight) of 0.9% saline until the resultant brei would pass through a 23-gauge hypodermic needle. Each animal was then injected in both gastrocnemii with 0.2 ml. of the suspension. Treatments were started three days after the inoculations. At this stage the tumours were just palpable. In every experiment all rats had palpable tumours at the start. Protamine-zinc insulin (P.Z.I.) was injected once daily at 3 p.m. Crystalline glucagon suspended in 0.9% saline was administered subcutaneously at 9 a.m., 3 p.m., and 9 p.m. The rats were sacrificed after 10 to 15 days of treatment. The back legs were skinned, carefully disarticulated at the hip-joint, and removed. Tumour weights were determined by subtracting from the weight of the tumour-bearing leg the average weight of the normal hind limb in rats of the same size. The doses of insulin and glucagon and other relevant data are given in the Table.

Results

The results of the experiments are also presented in the Table. In Experiment 1 the administration of insulin inhibited the growth of the tumour by 10%, while in

*On leave of absence from Professor J. P. Hoet's Department, University of Louvain, Belgium.

†Our former colleague, Dr. Spencer Monroe, now of the Sloan-Kettering Institute for Cancer Research, has recently discussed with us his observations on the dramatic inhibition by insulin of the growth of Rous sarcoma in chickens.

Experiment 5 no inhibition was discernible. In a large series of other trials not reported here, insulin consistently produced a small but significant slowing of the tumour growth. This inhibition occurred only when the food intake of the treated animals was restricted to the level of the controls.

The retardation of growth of the tumour induced by glucagon alone has varied from 20 to 40%. This inhibition can be attributed, in part, to the reduction in food intake and the adverse effect of glucagon on the growth of the rat as a whole (Salter *et al.*, 1957b). Although the rats treated with both insulin and glucagon lose less weight than animals given glucagon alone, inhibitions of tumour growth of 60–70% have been obtained invariably. The inhibition is not therefore proportional to the weight loss. In each experiment the carcinostatic action of the combined therapy has been much greater than the sum of the individual effects of the two substances.

Discussion

The data show that both insulin and glucagon produce some inhibition, which is, on the average, about 10% for insulin and approximately 30% for glucagon. Together they exert from 60 to 70% inhibition of growth of this particular tumour (Figs. 1 and 2).

We have thus far only established that the inhibition persists while insulin and glucagon are being administered. Cessation of treatment is followed by resumption of growth of the tumour. There has been a suggestion in a few cases that a prolonged remission may have taken place, but there is no proof as yet that this can actually be made to happen.

Hypoglycaemia still presents a serious problem, but the experience we have gained enables us to control the level of blood sugar better than was possible initially. A long-acting glucagon would be of great value in these studies.

If we consider for the moment only the control animals and those which have received insulin and glucagon together there have been in all 67 controls and 77 treated with the two substances. The inhibition of tumour growth produced by glucagon and insulin together has been remarkably consistent, but a great deal of further work will have to be done on this tumour and on others to determine the maximum extent and duration of the inhibition and the frequency with which it takes place in various species of animals. Dr. E. S. Goranson, of the Ontario Cancer Institute, working with one of us (J. M. S.), has already repeated our experiment, and has found that an extensive inhibition (80%) is exerted by insulin and glucagon together on the growth of the Novikoff tumour in rats. There was a negligible difference in the weight of the control and test animals at the end of the experiments. Studies of various other tumours are under way.

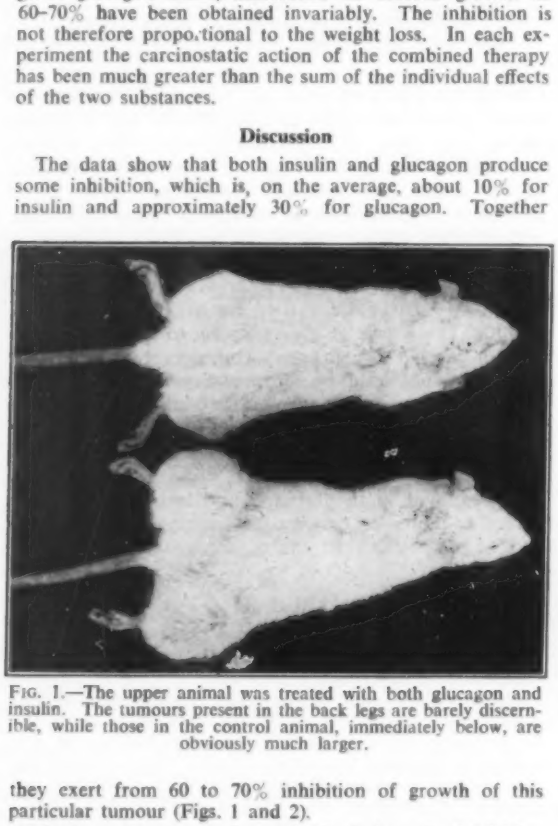

FIG. 1.—The upper animal was treated with both glucagon and insulin. The tumours present in the back legs are barely discernible, while those in the control animal, immediately below, are obviously much larger.

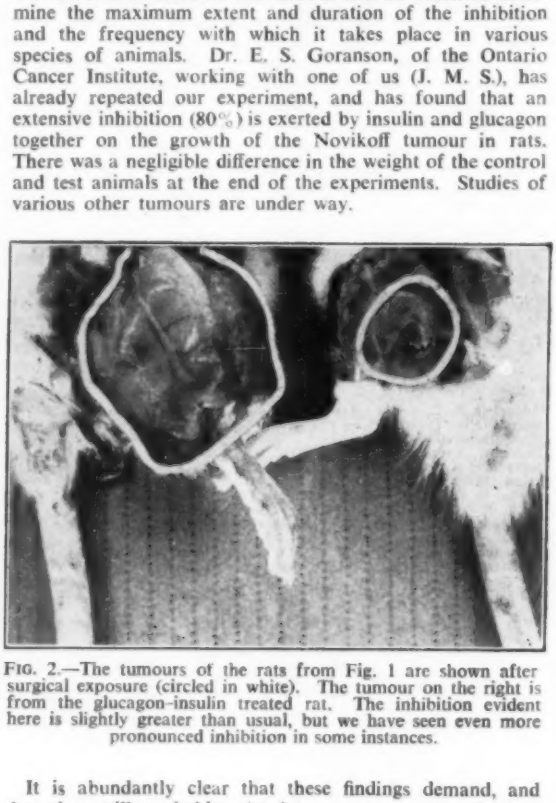

FIG. 2.—The tumours of the rats from Fig. 1 are shown after surgical exposure (circled in white). The tumour on the right is from the glucagon–insulin treated rat. The inhibition evident here is slightly greater than usual, but we have seen even more pronounced inhibition in some instances.

It is abundantly clear that these findings demand, and that they will probably stimulate, an even more vigorous exploration of the metabolic effects of insulin and glucagon given together. No attempt will be made here to review the controversial literature on this subject. If glucagon supplements the peripheral action of insulin on normal

Results of Experiments

Exp. No.	Treatment	No. of Animals Initial	No. of Animals Final	Days' Duration	Av. Daily Food Intake (g.)	Final Wt. (g.)	Wt. Change (g.)	Tumour Wt. (g. S.E.)	Inhibition (%)
1	None	25	25	10	12·8	156	+14	13·4 ± 0·42	10
	P.Z.I. (1·6 u. day)	50	35		12·8*	154	−16	12·0 ± 0·33	
2	None	25	25	12	10·3*	151	+3	16·4 ± 1·00	20
	Glucagon (150 μg. day)	25	25		10·3	142	−10	13·1 ± 0·78	
3	None	25	20	15	9·5*	138	−6	18·2 ± 2·10	27
	Glucagon (300 μg. day)	20	20		6·8	111	−29	13·2 ± 1·00	
	(300 μg. + P.Z.I. 3 u. day)	50	28†		9·5	129	−13	6·1 ± 1·18	67
4	None	20	20	10	10·5*	148	−5	13·5 ± 1·67	32
	Glucagon (900 μg. day)	20	20		5·6	116	−39	9·2 ± 0·88	
	(900 μg. + P.Z.I. 3 u. day)	40	25†		10·5	132	−18	5·4 ± 1·35	60
5	None	27	27	10	10·1	159	−10	7·0 ± 1·12	40
	P.Z.I. (1·6 u. day)	30	16		11·6*	150	−3	7·0 ± 0·81	
	Glucagon (210 μg. day)	25	22		9·4	121	−33	4·1 ± 0·93	
	(210 μg. + P.Z.I. 1·4 u. day)	34	24†		10·3	130	−18	2·1 ± 0·48	70

* Food intake restricted to this amount. † All deaths due to hypoglycaemia. Figure represents weight of carcass exclusive of tumour.

tissue, the effects of the two together in "starving" the tumour may be supplementary. Equally plausible suggestions may be based on the possible katabolic effects of glucagon on the tumour itself. Both mechanisms could be involved.

The field of tumour growth is notorious for the frequency of pitfalls. We have seen no indication that the effect we are investigating is due to a contaminating infectious agent or to other artifacts. These may, of course, emerge later and necessitate a change in the interpretation of our findings. We have obtained glucagon from two sources—Indianapolis and Toronto. The various lots of insulin have been made in Toronto.

It is obvious that, if this phenomenon of the extensive inhibition of tumour growth by insulin and glucagon together is observed in a large number of other tumours in various species of animals, a clinical trial of the substances may become very tempting. Some aspects of the investigation would be easier to control in the hospital than in the experimental laboratory. Clinically the two substances *could* be given by continuous intravenous drip and the hypoglycaemia which has plagued us could be detected at an early stage. Frequent blood-sugar estimations have not been considered advisable in the small animals. A sufficient number to establish low blood sugar as the cause of death in the insulin-treated animals which succumbed have been made. A great deal more should be learned in experiments on animals before any clinical study is seriously considered. An inhibition which persists only during the administration of the substances would be of limited clinical interest. The obvious possibility of using other substances to supplement the inhibition produced by insulin and glucagon is being explored.

We are indebted to Mrs. H. Viilup, Mrs. C. Hooper, and Mr. Gunther Brunet for their efficient technical assistance. This work has been supported in part by funds from the Foster Bequest of the University of Toronto and the National Research Council of Canada. We wish to thank the Connaught Medical Research Laboratories for the insulin and some of the glucagon which we have used. Our major source of glucagon has been Eli Lilly and Company.

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Dr. A. J. DALZELL WARD, medical director of the Central Council for Health Education, said at a recent press conference on the dangers of the common housefly, "Eggs laid last autumn are now hatching out. It takes about 12 days for the egg to hatch and another 12 days to reach maturity. During its brief life the housefly can lay about 900 eggs. Within a couple of months or two generations, therefore, some 800,000 (certainly half a million) flies can come from one fly. In other words one fly can have 800,000 grandchildren." Dr. Ward went on to describe prophylactic measures against the housefly. Obviously the best way to stop this menace to health was to prevent them breeding, he said. The lids of dustbins should be tight and not battered. The bottoms of dustbins should be kept clean and dry, and if possible sprayed with insecticide, preferably one containing D.D.T. It was a good thing to line the bottoms of dustbins with newspaper and renew this whenever they were emptied. As much rubbish as possible should be burned and the remainder, if burning was not possible, kept wrapped and covered until disposed of.

The housefly could and did travel as much as 10 or 12 miles (16–20 km.) from its breeding-place.

OOPHORECTOMY IN BREAST CANCER

AN ATTEMPT TO CORRELATE CLINICAL RESULTS WITH OESTROGEN PRODUCTION

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The treatment of metastatic breast cancer by surgical castration is the oldest rational method of palliation for this disease (Beatson, 1896). In the series reported by Thomson (1902) and Lett (1905) objective signs of growth regression in pre-menopausal women were observed in 25% of cases. On the other hand, and in sharp contrast, growth regression was limited to a single instance in a series of 25 post-menopausal women.

From 1910 onwards the usefulness of surgical castration was seriously questioned. For over thirty years it was generally discredited, and it was not reinstated until 1942 (Farrow and Adair, 1942) and Beatson's original and cautious claims were confirmed (Adair *et al.*, 1945; Sicard, 1947; Dargent, 1949). Objective remissions in post-menopausal cancer were again shown to be very uncommon.

The therapeutic purpose of surgical castration in pre-menopausal breast cancer is to arrest the progress of the disease by removing the source of ovarian oestrogen production. The palliation induced by this surgical manœuvre is clearly and intimately related to the regressions which are frequently observed during the "physiological castration" of a natural menopause in breast cancers which, arising during the pre-menopausal period, have already metastasized by the time the patient enters the menopausal phase (Clemmesen, 1948; Hadfield and Holt, 1956).

Laboratory studies of the effectiveness of oophorectomy in abolishing oestrogen production have not been numerous. Bio-assays or biochemical estimations of urinary oestrogens have been reported by Smith and Emerson (1954), Dao (1953), Bulbrook and Greenwood (1957), and McBride (1957), and studies of vaginal cytology were published by Struthers (1956). These investigations revealed that, whilst surgical castration does not abolish the excretion of oestrogens, it does significantly reduce the excretion in pre-menopausal women.

None of the above authors attempted to correlate the immediate and long-term fluctuations in urinary oestrogens with the clinical consequences of the operation. In the present communication this correlation has been attempted.

Material and Methods

All clinical regressions recorded have been based exclusively on observable objective improvement in superficial lesions or in deep lesions visualized by radiography, and all clinical assessments were made without prior knowledge of the biochemical estimations.

Oestrogen-excretion studies were carried out in hospital. Patients were divided into two groups. Those

in the first group had been oophorectomized before this investigation began and no pre-operative oestrogen levels were available. In the second group pre- and post-operative values were determined and the change in oestrogen excretion induced by the operation could be clearly defined.

After discharge all patients attended hospital at monthly intervals, whenever possible bringing a 24-hour specimen of urine. Some were readmitted for several days for clinical assessment and further oestrogen estimations. In a few cases the 24-hour urine specimen was collected from the patient's home. All patients were warned against the use of the several aperients which interfere with oestrogen analysis.

Vaginal smears were taken from the majority of patients and were graded as showing high, moderate, or low oestrogenic activity.

Chemical Methods.—Urinary oestrone, oestradiol-17β, and oestriol were measured by the method of Brown (1955a) or by the modification proposed by Brown, Bulbrook, and Greenwood (1957a). Results are expressed in μg./24 hours for each oestrogen, or as their sum. Analyses are shown as zero when the amounts of each oestrogen were less than the calculated limits of sensitivity of the method (Brown, Bulbrook, and Greenwood, 1957b). In Case 10, 17-oxosteroids and 17-oxogenic steroids were estimated by the methods of Norymberski, Stubbs, and West (1953) and Gibson and Norymberski (1954), and pregnanediol by the method of Klopper, Michie, and Brown (1955). The results of both analyses are expressed in mg./24 hours.

1. Clinical Effects and Hormone Excretion After Oophorectomy in Pre-menopausal Women

All patients in this group had a regular menstrual history up to the time of operation. Analyses were carried out on 230 urine specimens from 24 patients in whom progressive metastatic breast cancer had developed after oophorectomy. The mean daily amount of oestrogen was calculated for each patient. These amounts showed no correlation with the time after oophorectomy, and the amounts shown in Table I are the overall means for the 24 patients studied from 1 to 60 months after operation.

TABLE I.—*Oestrogen Levels 1 to 60 Months After Oophorectomy in 24 Pre-menopausal Women (230 Analyses)*

	Oestrone	Oestradiol-17β	Oestriol	Total
Arithmetical mean ..	1·8	0·6	2·9	5·3
Standard deviation ..	1·0	0·8	2·2	2·6

Results expressed in μg./24 hours.

Table I shows that in this group of women the level of oestrogen excretion was much lower than has been found during the normal menstrual cycle.

Four patients treated by oophorectomy for metastatic breast cancer were studied individually at intervals after operation. These patients had shown a regular menstrual history up to the month of operation. In two cases pre-operative oestrogen levels were not estimated, and it was assumed that these were within the normal range (Brown, 1955b). The detailed results are shown in Figs. 1 to 3.

Case Reports

Case 1 (Fig. 1).—This patient was a single woman aged 36. Eleven months after mastectomy, metastases appeared in the ribs, spine, and pelvis ; no ovarian or other soft-tissue deposits were detected. Bilateral oophorectomy was carried out. Oestrogen analyses were started two weeks after operation, and up to one month after operation the mean amount of oestrogen was only 2.8 μg./24 hours. A substantial fall in oestrogen excretion from the pre-operative level may be assumed to have taken place accompanied by objective

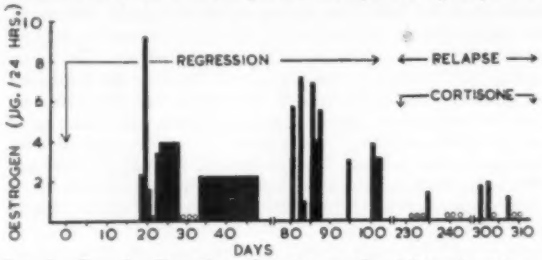

FIG. 1.—Case 1. Excretion of oestrogen after bilateral oophorectomy. In all figures the day of operation is marked with a vertical arrow. Oestrogen excretion is shown as total oestrogen —the sum of the oestrone, oestradiol-17β, and oestriol values. In Figs. 1–6 each vertical column gives the mean of a duplicate determination on a 24-hour specimen of urine. Open circles on the abscissa indicate no detectable oestrogen.

remission of the disease for four months following operation. Intermittent analyses from two to three months showed an increase in the mean oestrogen level to 3.9 μg./24 hours. The patient was readmitted to hospital seven months after oophorectomy, and cortisone therapy was initiated, and for a period of three months only trace amounts of oestrogen were detected. In spite of this, from the fourth to the tenth month after oophorectomy there was progressive growth in the skeletal metastases.

Case 2 (Fig. 2).—This patient, aged 53, married, had been menstruating regularly until 10 to 12 months before she was first seen ; during that time she had serious menorrhagia.

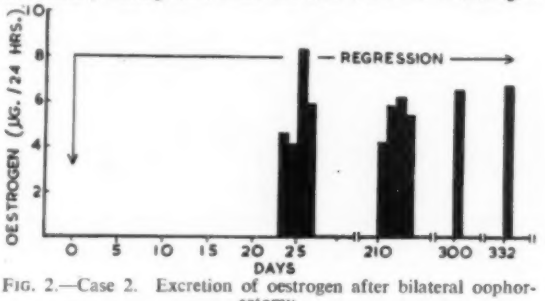

FIG. 2.—Case 2. Excretion of oestrogen after bilateral oophorectomy.

On admission she had gross pseudo-inflammatory malignant extension in the left breast, hard axillary glands on the same side, and the liver was palpable one fingerbreadth below the costal margin. No skeletal metastases were detected. There were multiple uterine fibromyomata. Hysterectomy and bilateral oophorectomy were performed. Examination of the liver at operation showed multiple metastases in the right lobe. The mean total oestrogen in the first month after oophorectomy was 5.8 μg./24 hours. Analyses at 7, 10, and 11 months later showed similar values, suggesting that at no time had oestrogen excretion reached zero. Over this period the breast became shrunken and softer, the skin reaction faded, and the nodes decreased in size.

Case 3 (Fig. 3).—This patient was aged 54 and married. Over the previous eight years, and after a left radical mastectomy, the intermittent appearance of clavicular, intercostal, sternal, costal, and supraclavicular swellings had been treated by deep *x* rays. When admitted to hospital she had pelvic bone metastases and a left pleural effusion. Admission interrupted an otherwise regular history of menstruation. The vaginal smear indicated high oestrogenic activity. Urinary excretion of oestrogen was irregular but showed a normal excretion pattern of the individual oestrogens and a total amount within the normal range (Brown, 1955b). 17-oxosteroid excretion was normal and relatively constant at 3.4 mg./24 hours. Operation revealed metastatic deposits in both ovaries. Oophorectomy produced an arrest in growth but no objective regression for a period of three

months, associated with a reduction in mean oestrogen excretion from 15.5 to 3.9 μg./24 hours, and a change in the appearance of the vaginal smear from high to moderate activity in the first two months after operation. The pre-operative lesions were virtually unchanged over the three-

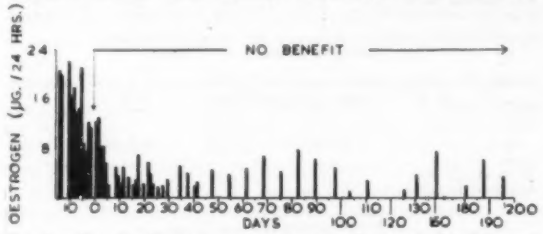

FIG. 3.—Case 3. Excretion of oestrogen before and after bilateral oophorectomy.

months period and a return to active growth and the reappearance of other skeletal secondaries was preceded by a slight rise in oestrogen excretion (5.3 μg./24 hours) and a return of the vaginal smear to one of high oestrogen activity. Intermittent analyses from the fourth to the sixth month after operation showed an irregular excretion around a mean value of 3.2 μg./24 hours. The patient died seven months after operation. Post-mortem examination revealed diffuse carcinomatosis; secondary deposits were found in the adrenal glands.

Case 4.—This patient, aged 44, married, had a history of recurrence of growth after a previous mastectomy similar to that described in Case 3. Oestrogen excretion before operation showed a similar picture—irregular excretion but a normal pattern and total amount; the mean pre-operative level was 14.4 μg./24 hours. Clinically, oophorectomy had no effect, but regression of the lesions was obtained by irradiation from one to three months after operation. Oestrogen levels were investigated only at the fourth month. At this time oestrogen was still present, although in amounts (3.3 μg./24 hours) well below the mean pre-operative level. The patient died seven months after operation. Post-mortem examination showed diffuse carcinomatosis.

Summary of Findings in Pre-menopausal Group

The mean excretion of Cases 3 and 4 before operation was about 15 μg./24 hours. Similar figures have been given for pre-menopausal women with breast cancer (Birke *et al.*, 1958) and for normal women (Brown, 1955b). The results shown in Table I, and Figs. 1 to 3, afford further evidence that oophorectomy in pre-menopausal women removes a major source of oestrogen production. Although well marked in Cases 3 and 4, the reduction in oestrogen excretion was not accompanied by objective remission of the disease.

The range and mean levels of oestrogen excreted after oophorectomy demonstrate that adrenal secretion of oestrogen is always detectable after operation and can vary within wide limits. The results obtained in the first few days after operation (Case 3) suggest that the adrenal glands contribute to excretion before oophorectomy, and this component may be temporarily increased by operative stress.

The finding that adrenal secretion of oestrogen is usual after oophorectomy would afford at least a rational explanation for the clinical failure of the operations in Cases 3 and 4, but remission of the disease was obtained in Cases 1 and 2, although oestrogen was always detectable in the urine. The levels of oestrogen in the latter cases do not differ from the levels found in the group with progressive disease (Table I).

2. Clinical Effects and Hormone Excretion After Oophorectomy in Menopausal Women

For the purpose of this paper we have defined as "menopausal" those women who last menstruated less than a year before oophorectomy. A group of six patients who had been oophorectomized for metastatic breast cancer during the menopause was investigated. Oestrogen studies after oophorectomy were made at a time when the disease had recurred, from 1 to 24 months after operation, in these patients. Table II shows the mean oestrogen levels based upon the analysis of 50 urine specimens from the six patients. The amounts and pattern of oestrogen excreted do not differ from that found in the pre-menopausal group (Table I).

TABLE II.—*Oestrogen Levels 1 to 60 Months After Oophorectomy in Six Menopausal Women (50 Analyses)*

	Oestrone	Oestradiol-17β	Oestriol	Total
Arithmetical mean ..	1·8	0·4	3·9	6·1
Standard deviation ..	1·5	0·5	5·3	6·4

Results expressed in μg./24 hours.

More detailed studies were made on four menopausal patients with metastatic breast cancer.

Case 5 (Fig. 4).—This patient, aged 45, married, had a previous history of mastectomy, with the later appearance

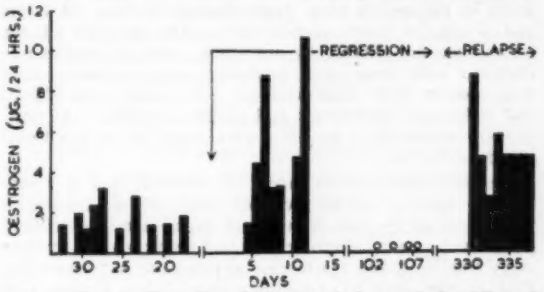

FIG. 4.—Case 5. Excretion of oestrogen before and after bilateral oophorectomy.

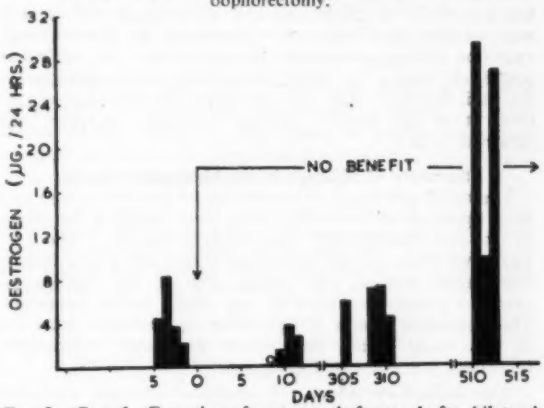

FIG. 5.—Case 6. Excretion of oestrogen before and after bilateral oophorectomy.

of supraclavicular nodes. These and subsequent pelvic bone deposits were treated by deep *x*-ray therapy. Periods were regular until nine weeks prior to oophorectomy but had ceased at this time incidental to the deep *x*-ray therapy. Excretion of oestrogen was very low, but oophorectomy occasioned a transient though pronounced rise in excretion. An objective regression of five months' duration followed oophorectomy. No oestrogen could be detected three months after operation. The disease progressed from the sixth month until death, 13 months after operation. Oestrogen excretion during this period had returned to a mean value of 5.2 μg./24 hours, above the pre-operative level of 1.9 μg./24 hours.

Case 6 (Fig. 5).—This patient, aged 55, married, had a six-months history of a lump in the breast with involvement of the axilla. Treatment by deep *x* rays to the breast and axilla was started. Menstruation had been regular until six months before operation. Just before operation the

vaginal smear showed moderate to high oestrogen activity, but the total amount of oestrogen was low. The immediate effect of oophorectomy was difficult to evaluate, since deep *x*-ray treatment was continued. A very low level was found in the first month after operation. Clinically some subjective improvement was noted for the first post-operative month, but by the third month deep *x*-ray treatment to the breast and axilla was resumed. Subsequent progression of the disease, with the appearance of new lesions, was noted over a period from the fifth to the seventeenth month after operation. Oestrogen excretion had increased by the tenth month, and a further very marked rise was shown in the seventeenth month, a few days before death.

Case 7.—This patient was single, aged 42. Fifteen months after mastectomy and deep *x*-ray treatment for carcinoma of the right breast she developed a pleural effusion and metastases in the spine, ribs, and pelvis. Pre-operative oestrogen (2.6 μg./24 hours) and 17-oxosteroid excretion (1 mg./24 hours) were low. At operation both ovaries contained secondary deposits. Both oestrogen and 17-oxosteroid excretion were raised above the pre-operative levels in the month after oophorectomy (7.6 μg./24 hours and 5 mg./24 hours respectively). The progress of the disease was not affected by operation. Some palliation was obtained with deep *x*-ray treatment, but the patient died four months after oophorectomy with widespread pleural and pulmonary metastases and skeletal deposits. At post-mortem examination deposits were found in both adrenal glands.

Case 8.—This patient, aged 51, married, had a seven-months history, before oophorectomy, of an inoperable carcinoma of the left breast with gross skin and axillary node involvement. Improvement had been obtained by deep *x*-ray treatment and the disease appeared to be responding. Four months prior to operation vaginal smears showed high oestrogenic activity. At operation oestrogen excretion was not high (3.6 μg./24 hours) and an atypical fall to zero was obtained up to the time of discharge, the 17-oxosteroid excretion being unchanged by operation. An objective regression lasting for three years followed oophorectomy, but as it has been impossible to carry out further investigations it is not known whether oestrogen secretion has returned or not.

Summary of Findings in the Menopausal Group

The oestrogen levels of the individual patients before and after operation do not differ from those found in the group of patients studied after operation (Table II). The pre-operative levels are low compared with those found in pre-menopausal women, and suggest that in the menopausal cases an ovarian contribution was absent before operation. The immediate effects of operation on oestrogen excretion in this small series show three variations: unchanged, increased, and decreased excretion.

The immediate effects of oophorectomy on oestrogen secretion would appear to be determined by the degree of operative stress and the individual reaction to this. In the two cases followed for some time after operation the immediate effects were not maintained. In Case 5 the excretion fell to zero over a period of remission, and rose with the progression of the disease; in Case 6 the oestrogen excretion, unchanged by operation, rose as the disease progressed.

The four cases show a clear association between the effects of oophorectomy on oestrogen excretion and the clinical state. The operation was not effective in two cases showing an increased or unchanged excretion, but objective regressions were produced in the two cases in which oestrogen excretion fell to zero. In one of the latter, oestrogen excretion returned when the patient relapsed.

3. Clinical Effects and Hormone Excretion After Oophorectomy in Post-menopausal Women

We have defined as "post-menopausal" those women who had not menstruated for at least one year before

TABLE III.—*Oestrogen Levels 2 to 8 Years after the Menopause in 16 Post-menopausal Women (81 Analyses)*

	Oestrone	Oestradiol-17β	Oestriol	Total
Arithmetical mean ..	1·8	0·9	2·4	5·0
Standard deviation ..	1·3	1·3	2·1	2·6

Results expressed in μg./24 hours.

TABLE IV.—*Oestrogen Levels 2 to 36 Months After Oophorectomy in Six Post-menopausal Women (31 Analyses)*

	Oestrone	Oestradiol-17β	Oestriol	Total
Arithmetical mean ..	1·8	0·9	3·5	6·3
Standard deviation ..	1·0	0·6	1·9	2·7

Results expressed in μg. 24 hours.

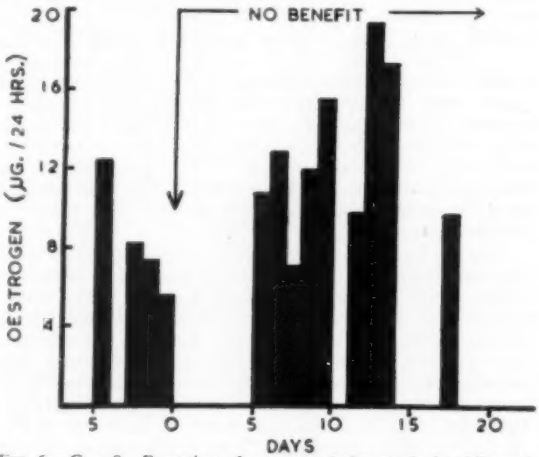

FIG. 6.—Case 9. Excretion of oestrogen before and after bilateral oophorectomy.

oophorectomy. A comparison of the oestrogen excretion levels of a group of post-menopausal women with metastatic breast cancer with the readings from a similar group after oophorectomy shows that the results are the same in the two groups (Tables III and IV) and suggest that oophorectomy has no effect on oestrogen excretion.

Four cases studied before and after oophorectomy conform to this general pattern, and in these no regression of the disease was obtained. In addition, three of the four cases showed an increased excretion of oestrogen within the first weeks after operation. Case 9 illustrates the general findings in this group.

Case 9 (Fig. 6).—The patient, aged 52, married, had a one year's history of inoperable breast cancer treated by deep *x* rays, and subsequently by oophorectomy for skeletal metastases, with no effect. The disease slowly progressed, and by the ninth month after opera-

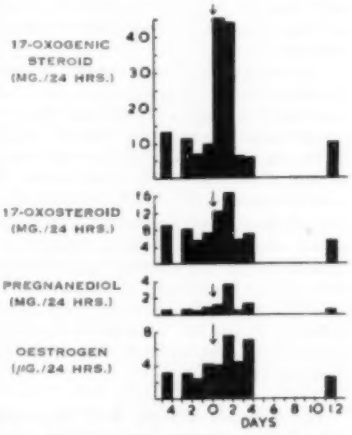

FIG. 7.—Case 10. Excretion of steroids before and after mastectomy. Each vertical column gives the mean of a duplicate determination for oestrogen, pregnanediol, 17-oxosteroid, and 17-oxogenic steroid on a 24-hours specimen of urine.

tion the breast had ulcerated and the bone metastases had spread. The patient died 11 months after operation. The immediate effects of operation are shown in Fig. 6. The mean pre-operative level was 9.2 μg./24 hours, and in the first two weeks there was a marked adrenal reaction to operation, the mean level being 12.7 μg./24 hours.

A more detailed study of operative stress is shown in Case 10.

Case 10 (Fig. 7).—The patient, aged 56, married, was post-menopausal, had an operable breast cancer, and was treated by mastectomy only. The rise in oestrogen excretion was not marked and took place from the first to the fourth day after operation before reaching pre-operative levels. The increase in 17-oxosteroid, 17-oxogenic steroid, and pregnanediol excretion was more marked, and occurred on the first and second days after operation.

Summary of Findings in the Post-menopausal Group

As with the group of menopausal women, the immediate effect of oophorectomy may be an increase in oestrogen excretion due to operative stress. The overall effect of oophorectomy in the post-menopausal women is that both the clinical course of the disease and the oestrogen levels remain unaltered.

Discussion

The levels of urinary oestrogen found after oophorectomy in pre-menopausal, menopausal, and post-menopausal women with metastatic breast cancer are similar in amount and pattern to those of normal menopausal and post-menopausal women. It is only in pre-menopausal women that a post-operative fall invariably takes place. In all three groups there are considerable variations in the total amount of oestrogen excreted after operation, and the quantity varies from one patient to another and in each patient at different times. In many instances the levels approach those found in normal menstruating women. On the other hand, oestrogen excretion is rarely recorded as being below 1 to 1.5 μg./24 hours, the arbitrary limit imposed by the sensitivity of the chemical method used.

The failure of surgical castration to reduce oestrogen excretion in menopausal and post-menopausal women is probably related to variations in the relative amounts of oestrogen contributed by the ovary on the one hand and the adrenal on the other. No fall in oestrogen could be expected if the ovarian contribution were negligible, whilst a post-operative suppression of ovarian oestrogen production could be offset by an increase of adrenal oestrogen production, such adrenal overactivity being a possible result of operative stress. This interpretation of our clinical and biochemical observations in menopausal and post-menopausal women affords some justification for further endocrine ablation as the subsequent treatment of choice. Adrenalectomy would be expected to accomplish both a steep fall in oestrogen excretion and a reduction below a critical level, which in all probability varies from patient to patient.

The removal of the pre-menopausal ovaries, although reducing oestrogen excretion, is not always accompanied by regression of the disease. There are several possible explanations for this observation, but no definite conclusions can be drawn from the data presented in this paper. For example, the beneficial effects of oophorectomy in some pre-menopausal women may depend upon the extent of the post-operative fall in oestrogen production. This is unlikely to be constant in all patients submitted to oophorectomy, since it depends upon the relative contributions of the ovaries and adrenal glands pre-operatively, the stressing effect of the operation on adrenal secretion, and the "resting" level of adrenal oestrogen production. Each of these factors is known to vary widely from patient to patient (Brown, 1958; Birke *et al.*, 1958; this paper), and this would provide an adequate basis for the variation to be expected in the extent of the fall in oestrogen production after oophorectomy.

Alternatively, the clinical success of oophorectomy may depend upon the reduction of circulating oestrogen below a critical level irrespective of the pre-operative level. If this be attained regression might follow. On the other hand, such a period of growth remission could be interrupted by a period of progressive growth if adrenal oestrogen production were increased by a sustained episode of traumatic stress. The well-attested variation in the capacity of the adrenal glands to take over oestrogen production after surgical castration has already been emphasized and the absence of oestrogen in two cases in objective remission may well be significant examples of this phenomenon.

For this discussion we have used the simple example of oestrogen reduction. It must be appreciated that the effects of oophorectomy, like the effects from the natural menopause, are not those of simple oestrogen removal or reduction, but involve a complex of changes which result in a gross disturbance of both adrenal and pituitary function in addition. It is probable that tumour regression is not related to simple changes in oestrogen, but is related to the whole complex of changes by alteration in oestrogen, progestogen, and pituitary hormone variation.

Summary

The effects of bilateral oophorectomy upon the clinical state and oestrogen excretion have been studied in patients with metastatic breast cancer.

Objective remission in pre-menopausal women after oophorectomy was not invariable, despite a fall in oestrogen excretion. Possible reasons for this are presented.

Objective remission in menopausal and post-menopausal women appeared to be unlikely unless the ovarian contribution of oestrogen was significant and adrenal secretion of oestrogen unaffected by operation.

Oestrogen derived from the adrenal glands appears to be present in all patients after oophorectomy. The removal of this source of production by further endocrine surgery appears to be indicated when oophorectomy fails to arrest the progress of the disease.

We are grateful to the surgical staff and the staff of the radiotherapy department of St. Bartholomew's Hospital for allowing us to investigate patients under their care, and particularly to Professor Sir James Paterson Ross, who has also been most helpful with his advice and criticism.

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ADRENALECTOMY IN BREAST CANCER

AN ATTEMPT TO CORRELATE CLINICAL RESULTS WITH OESTROGEN PRODUCTION

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Continued excretion of oestrogen produced by the adrenal cortex occurs after oophorectomy in the majority of women with breast cancer. In 1945 Huggins and Scott performed bilateral adrenalectomy in four cases of advanced breast and prostatic cancer in an attempt to remove the second source of oestrogen production from the body. One patient survived for 116 days in a hypo-adrenal state, with some objective improvement in skeletal metastases. When cortisone became available the operation was carried out in 18 cases (Huggins and Bergenstal, 1952). Seven were women suffering from cancer of the breast, and clinical improvement was induced in all of them. The results stimulated great interest in the subject, and since 1952 many series of cases have been reported. It seems that bilateral adrenalectomy can play a definite and sometimes valuable part in the palliative treatment of breast cancer.

When adrenalectomy fails to induce a growth regression in breast cancer, oestrogen independence is generally assumed to be the cause. A second possible explanation was suggested by the reports of Scowen (1955) and of Struthers (1956), who found that oestrogen secretion could continue after bilateral adrenalectomy, as judged by the appearance of the vaginal smear. This was an unexpected result at that time, but these findings have since been confirmed by urinary oestrogen estimations, using Brown's (1955) chemical method (Greenwood and Bulbrook, 1956; Bulbrook and Greenwood, 1957), and also by biological assay (Dao, 1957; Bulbrook *et al.*, 1958c).

We have been unable to find any published reports in which an attempt has been made to correlate oestrogen excretion with the patient's clinical state after adrenalectomy. This paper reports such a survey of 13 cases of metastatic breast cancer in women treated by bilateral adrenalectomy.

Methods

Chemical.—The chemical method of Brown (1955) for the determination of urinary oestrone, oestradiol-17β, and oestriol was used initially. This technique gives an underestimate of the amount of oestradiol-17β and oestriol when cortisone is administered to the patient. A minor modification removes this source of interference, but a variety of drugs and aperients can lead to an overestimate of the amount of oestrogen in the urine (Brown *et al.*, 1957). Oestrogen excretion is recorded as zero when the amounts detected are below the limit of sensitivity of the chemical method. This is an arbitrary limit which can be lowered by the more sensitive biological assay (Bulbrook *et al.*, 1958c).

Clinical.—In this series regression is defined as objective improvement in either surface lesions or in deep metastatic lesions visualized by radiography. Clinical assessments were carried out without prior knowledge of the biochemical results. The patient's age quoted is that at the time of adrenalectomy. Thirteen patients with metastatic breast cancer were studied; in seven cases urinary oestrogen estimations were carried out before and after adrenalectomy and at intervals after operation; in the remaining six, only post-operative estimations were carried out.

The cases are divisible into two groups: those in objective remission, and those in relapse.

Oestrogen Excretion in Patients During Objective Remission

Of the 13 patients studied, only three were in remission at the time the oestrogen estimations were carried out. The detailed results are described below.

Case 1 (Fig. 1).—The patient, aged 48, was married. Ten years after left radical mastectomy the wound ulcerated. Seven years later, when she was 46 years old, she was treated by oophorectomy, with some benefit for six months, although the wound did not completely heal. Two years later there was gross ulceration of the chest wall spreading into the axilla; there was no evidence of distant metastases. Bilateral adrenalectomy was performed and induced

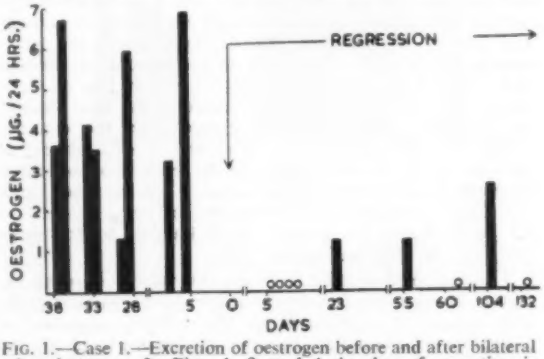

FIG. 1.—Case 1.—Excretion of oestrogen before and after bilateral adrenalectomy. In Figs. 1, 2, and 4 the day of operation is marked with a vertical arrow. In all Figs. the oestrogen excretion is shown as total oestrogen—the sum of the oestrone, oestradiol-17β, and oestriol values. Each vertical column gives the mean of a duplicate determination on a 24-hour specimen of urine. Open circles on the abscissa indicate no detectable oestrogen.

regression of the growth, which has been maintained for eight months. Before adrenalectomy the mean total oestrogen level was 3.7 µg./24 hours; after operation zero levels were frequent, with occasional small amounts of oestrogen found in some specimens of urine. At subsequent follow-up at intervals after operation, oestrogen was occasionally detected in the urine. Thus in this case regression of the tumour was associated with the virtual disappearance of oestrogen from the urine.

Case 2 (Fig. 2).—This patient, aged 42, married, underwent oophorectomy three and a half years after radical mastectomy because of the appearance of metastases in the left axilla and supraclavicular glands. There were no pulmonary or skeletal secondaries. The operation led to a short symptomatic regression, but skeletal secondaries ultimately developed. Two years and nine months after oophorectomy, bilateral adrenalectomy was carried out. An objective remission was induced. This lasted for four months, during which time a pathological fracture of the ulna healed and secondary deposits in the skull became smaller and calcified. During this period oestrogen excretion was reduced but not entirely abolished. Zero values were uncommon, and the mean total level of oestrogen over the first post-operative month was 1.9 µg./24 hours.

At a subsequent examination, eight months later, the disease was progressive, metastases being present in the clavicles, spine, lung, and brain. At this time oestrogen excretion had risen to a relatively high level and was persistent (mean total = 8.5 μg./24 hours). Two months before death—which occurred 11 months after adrenalectomy—only one

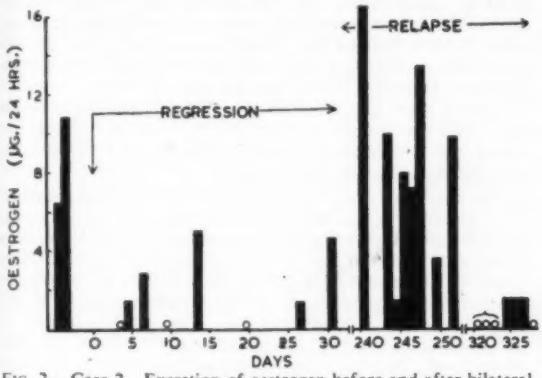

FIG. 2.—Case 2. Excretion of oestrogen before and after bilateral adrenalectomy.

of three urine specimens contained detectable amounts of oestrogen. This case illustrates the transition from regression to relapse. During the short remission oestrogen excretion was persistent and rose considerably in relapse until just before death.

Case 3.—From this patient, a married woman aged 46, no pre-operative specimens were obtained. A radical mastectomy was performed at the age of 45. Ten months later skeletal metastases developed, and at oophorectomy, which had no effect, liver secondaries were found. Adrenalectomy was carried out three months later and led to an objective regression of both skeletal and hepatic metastases. During the period of regression oestrogen estimations were carried out 15 and 40 months after operation. No oestrogen was detected in any of the 11 specimens analysed. Four years after adrenalectomy there was evidence of progressive disease. Seven analyses were carried out, and in only one was there detectable oestrogen (approximately 1.5 μg. of oestriol). Unlike Case 2, the transition from remission to relapse was not accompanied by a rise in oestrogen excretion.

In these three cases the period of remission was associated with either no detectable oestrogen (Case 3) or with a negligible and spasmodic excretion (Case 1). Case 2 shows that the continued excretion of oestrogen, admittedly small, is not incompatible with objective remission. Progression in this case was accompanied by a rise in oestrogen excretion but in Case 3 this did not occur.

Oestrogen Excretion in Patients During Relapse

This group includes patients whose oestrogen excretion was studied before and after adrenalectomy but who had no benefit from the operation, and those who were only studied when in relapse. Two examples are described in detail.

Case 4.—This patient, aged 51, married, was treated by radical mastectomy at the age of 51, when she was one year post-menopausal. Nine months later oophorectomy and adrenalectomy were carried out because of recurrence of the local growth. The operation led to the cessation of oestrogen excretion, but the patient died of progressive disease four months after operation. The oestrogen results are shown in Fig. 3.

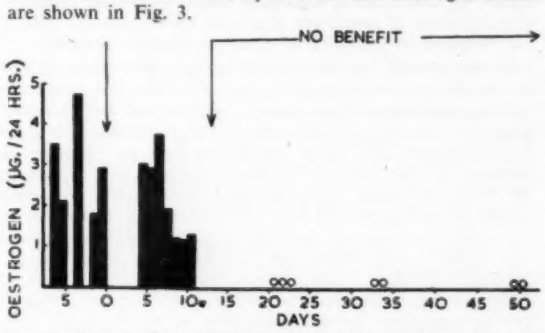

FIG. 3.—Case 4. Excretion of oestrogen before and after bilateral oophorectomy and adrenalectomy. The first vertical arrow indicates the time at which bilateral oophorectomy and single adrenalectomy was carried out; the second arrow indicates the time of removal of the second adrenal gland.

In a similar case (No. 6, see Table) with a very high post-oophorectomy oestrogen level (13.8 μg./24 hours), oestrogen excretion was abolished by operation, but no clinical effect was noted.

Case 5 (Fig. 4).—This patient, aged 38, married, was treated by oophorectomy at the age of 37, 20 months after mastectomy, because of multiple skeletal deposits. Four

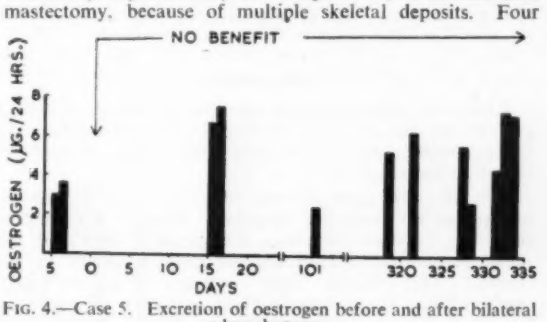

FIG. 4.—Case 5. Excretion of oestrogen before and after bilateral adrenalectomy.

*Oestrogen Excretion Before and After Bilateral Adrenalectomy**

Group	Case No. and Age	Pre-Adrenalectomy				Post-Adrenalectomy							
						In Remission				In Relapse			
		O	D	T	Total	O	D	T	Total	O	D	T	Total
1	1 (48)	1·5	0·0	2·2	3·7 (9)	0·5	0·0	0·0	0·5 (7)				
	2 (42)	4·5	1·4	2·8	8·7 (2)	1·3	0·6	0·0	1·9 (8)	0·9	0·7	3·0	4·6 (12)
	3 (46)					0·0	0·0	0·0	0·0 (11)	0·0	0·0	0·0	0·0 (7)
2	4 (51)	2·8	0·3	0·0	3·1 (5)								0·0 (7)
	5 (38)	1·8	1·4	0·0	3·2 (2)					0·9	0·9	3·6	5·4 (10)
	6 (43)	4·9	4·3	4·6	13·8 (4)					0·0	0·0	0·0	(2)
	7 (66)	1·0	0·0	2·2	3·2 (5)					0·5	0·0	1·3	1·8 (7)
	8 (44)									1·3	0·8	7·3	9·4 (24)
	9 (47)									0·9	1·0	0·4	2·3 (7)
	10 (37)									0·0	0·0	1·1	1·1 (4)
	11 (46)									0·0	0·0	0·0	0·0 (7)
	12 (52)									0·0	0·0	0·0	0·0 (5)
	13 (46)									0·0	0·0	0·0	0·0 (5)

*The case numbers are those referred to in the text; the age of the patient at adrenalectomy is given in parentheses in the first column. O, D, and T refer to oestrone, oestradiol-17β, and oestriol respectively, and the figures given are arithmetical means. Figures in parentheses in the columns headed "Total" refer to the number of estimations carried out. All results are expressed in μg./24 hours.

All patients had been previously oophorectomized, with the exception of Cases 4, 11, and 13, who were subjected to bilateral oophorectomy and adrenalectomy at the same time.

months of objective remission followed and a pathological fracture of the humerus consolidated. Thereafter the disease progressed and adrenalectomy was carried out. No benefit was obtained, and the patient died of progressive disease 22 months after operation. It can be seen from Fig. 4 that bilateral adrenalectomy had virtually no effect on oestrogen excretion.

A further seven patients were studied in relapse. In four oestrogen was found in the urine, in one case in remarkably high amounts—up to 50 μg./24 hours. This abnormal level of excretion was followed by a period when the patient excreted over 9 μg./24 hours. This level, subsequently confirmed by quantitative biological assay, is greater than the mean amount of oestrogen produced by the adrenal glands and excreted in the urine of post-menopausal women.

In the 10 cases described in this section, five either derived no benefit from adrenalectomy or, when the oestrogen estimations were carried out, were in relapse and not excreting detectable amounts of oestrogen. The remaining five were excreting oestrogen whilst the disease was progressing. A summary of the findings for the 13 patients is presented in the Table, in which the mean total pre-operative oestrogen values are given and the mean levels found in relapse or in remission are also shown. It must be pointed out that the mean figures should be accepted with some reserve. Reference to Figs. 1 and 2 shows the intermittent nature of oestrogen excretion after adrenalectomy, and from this it can be concluded that the estimation of the oestrogen content of single 24-hour specimens of urine may be misleading. Short periods, during which oestrogen excretion is relatively high, may be followed by periods during which little oestrogen can be detected. This phenomenon therefore reduces the value of a mean figure. Nevertheless, the table illustrates the mean excretion before operation and the extent to which adrenalectomy causes a diminution in excretion. The mean pre-operative figure is within the range given for post-menopausal women or oophorectomized women with cancer of the breast given in a previous paper (Bulbrook *et al.*, 1958a). Average oestrogen levels in remission are less than 1 μg./24 hours (total), with a considerable increase when the levels in relapse are considered.

Discussion

It must be emphasized that the series of patients described is small and that of a total of 13 cases six were studied only during relapse. Any conclusions based on the results must therefore be tentative.

It is clear that adrenalectomy reduces, even if it does not always abolish, oestrogen excretion. There is a significant difference between the mean pre-operative level and the mean post-operative level for the patients shown in the Table. This affords clear evidence that the post-oophorectomy or post-menopausal excretion of oestrogen described in a previous paper (Bulbrook *et al.*, 1958a) is of adrenal origin in the human (see Brown, 1958). Remission of the disease, however, does not always follow the reduction or abolition of oestrogen excretion.

It seems that continued oestrogen excretion is not necessarily exclusive of objective regression of the disease. The amounts excreted by Case 1 after operation were negligible and inconstant, but Case 2 showed a definite and persistent excretion. If this result can be confirmed by a wider study on more cases, the implication is that the cessation of secretion of hormones other than the oestrogenic steroids produced by the ovaries and adrenals may be decisive in causing the regression of human breast cancer. The complex nature of the dependence of normal breast growth on a group of hormones acting together is well established in experimental animals (see, for example, Lyons *et al.*, 1955; Hadfield, 1957), but such data are almost entirely lacking for the human. The participation of a pituitary factor is suggested by the finding that two patients (Cases 11 and 13) in relapse after adrenalectomy were without detectable oestrogen but obtained remission after subsequent hypophysectomy (Bulbrook *et al.*, 1958b).

Half the patients in relapse in this series showed continued excretion of oestrogen after adrenalectomy, compared with roughly one-third in a larger series studied without consideration of clinical state (Bulbrook and Greenwood, 1958). It seems unnecessary to postulate oestrogen independence of the tumour as the cause of the failure of treatment in these cases. In considering the six patients in relapse in whose urine no oestrogen could be detected, some caution must be used before continued tumour growth is ascribed to oestrogen independence or to dependence upon pituitary factors. With the use of the more sensitive biological assay (Bulbrook *et al.*, 1958c) it has been shown that oestrogen excretion may continue in some oophorectomized adrenalectomized patients, although in amounts not detectable by the chemical method.

The source of the continued oestrogen remains obscure. The literature describes the occurrence of microscopical ectopic adrenal tissue, but no macroscopic rests have been found after death in four of the patients in this series. One (Case 8) was excreting considerable amounts of oestrogen. Furthermore, Strong *et al.* (1956) could not elicit an increased oestrogen excretion by the administration of adrenocorticotrophin in adrenalectomized patients. On the other hand, Bulbrook and Greenwood (1958) have found that continued oestrogen excretion after adrenalectomy tends to be present with the continued excretion of androsterone and aetiocholanolone, compounds which are not considered to be derived from administered cortisone. This result therefore indicates that the probable source of the steroid hormone production is likely to be adrenal tissue; otherwise it is necessary to postulate an alternative source with adrenal-like properties.

It has also been suggested that the tumour itself may be responsible for the production of oestrogens. Chemically and biologically detectable amounts of oestrogens have been found in all cases in a series of adrenalectomized patients with diffuse carcinomatosis (Daniel and Mitchell, personal communication). This theory is supported to a certain extent by the results in this paper, which show that oestrogen excretion may be associated with progression of the disease. In a previous paper (Bulbrook *et al.*, 1958a) oestrogen excretion rose as the disease progressed in a patient following oophorectomy until, just before death, relatively enormous amounts of oestrogen were recorded (four times the mean post-oophorectomy level). These results could be interpreted as indicating tumour production of oestrogen. Similarly, in Case 8 (see Table) the mean oestrogen level after oophorectomy and adrenalectomy was almost twice that found for patients after oophorectomy alone. In this patient a careful search at post-mortem examination failed to reveal macroscopic adrenal rests. If the tumour itself produces oestrogen, this does not occur in all cases of progressive disease (see Cases 3, 4, 6, 11, 12, and 13 in the Table), where no oestrogens were detected by the chemical method.

Finally, oestrogen analyses of urine obtained from patients after adrenalectomy afford no reliable guide to the clinical state of individual patients. Every permutation may occur, remission or relapse being accompanied in some cases by oestrogen excretion, while in others no oestrogens were detectable. Only when the patients in this small series are considered as a group does it appear that there is a tendency for remission to be accompanied by low or zero excretion and for relapse to be associated with higher levels of excretion.

Summary

The effect of adrenalectomy on both the clinical state and oestrogen excretion has been studied in 13 women with metastatic breast cancer.

Bilateral adrenalectomy caused a marked reduction in the amount of oestrogen excreted, but complete abolition of excretion was not always achieved. However, continued oestrogen excretion did not exclude objective regression.

Conversely, progression of the disease might take place in spite of the fact that no oestrogen could be detected in the urine. In general, continued oestrogen excretion was found more often in cases in relapse than in remission.

We are grateful to the surgical staff and the staff of the radiotherapy department of St. Bartholomew's Hospital for allowing us to investigate patients under their care, and particularly to Professor Sir James Paterson Ross, who has also been most helpful with his advice and criticism.

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HYPOPHYSECTOMY IN BREAST CANCER

AN ATTEMPT TO CORRELATE CLINICAL RESULTS WITH OESTROGEN PRODUCTION

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In 1953 Luft and Olivecrona reported that hypophysectomy was an effective means of palliation in a significant proportion of cases of metastatic breast cancer. Subsequent work has confirmed these results (Luft and Olivecrona, 1955; Pearson *et al.*, 1955). The beneficial effects of the operation were ascribed to the inhibition of ovarian and adrenal function due to the removal of the relevant pituitary trophic hormones, and to the removal of those pituitary hormones which might have a direct influence on human breast cancer.

The technical difficulties in totally removing the pituitary gland are formidable, and reports on post-mortem findings suggest that complete removal is infrequently achieved (Hortling *et al.*, 1957; Luft *et al.*, 1958). Post-operative investigations of the living patients are therefore of value in deciding if removal has been complete; and, whilst methods are available for the bio-assay of pituitary gonadotrophin and for measuring the functional capacity of the thyroid, adrenals, and ovaries, it is possible that repeated oestrogen measurements provide reliable information on pituitary function following attempted ablation (Dodds *et al.*, 1956). It has been shown (Greenwood and Bulbrook, 1956, 1957) that many patients still excrete appreciable quantities of oestrogen in the urine after hypophysectomy, but no correlation of these or subsequent results with the clinical state and/or the post-mortem findings has been attempted.

The present paper reports an effort to correlate oestrogen excretion with the clinical state of 16 breast-cancer patients on whom hypophysectomy was performed.

Methods.—The clinical and chemical methods were exactly as described in previous papers (Bulbrook *et al.*, 1958a, 1958b).

In the 16 patients studied, oestrogen estimations were carried out before and after operation. The results have been divided into groups: the first showing oestrogen levels found in 11 patients who obtained regression at hypophysectomy, the second showing the oestrogen levels in the five patients who derived no benefit from surgical hypophysectomy. One in the latter group was a male. The ages given refer to age at hypophysectomy.

Oestrogen Excretion in Patients in Whom Objective Remission of Growth was Induced by Hypophysectomy

Of the 11 patients included in this group, five were post-menopausal, four had previously been treated by oophorectomy, and two by oophorectomy and adrenalectomy. All but two (Cases 1 and 11) had undergone radical mastectomy. Remission of the disease varied from 2 to 16 months after hypophysectomy, and in five patients remission has continued to the time of writing. Oestrogen studies were carried out before operation and at least one month after operation—with one exception, Case 4. The mean oestrogen levels were calculated from serial analyses of 24-hour specimens of urine. Table I summarizes the clinical and biochemical findings of the 11 patients studied in this section, and the salient features of the cases are considered in detail below.

Case 2 (Fig. 1).—This patient, aged 55, had a ten-years history of breast cancer treated in turn by mastectomy, deep *x*-ray therapy, and cortisone. At hypophysectomy, when

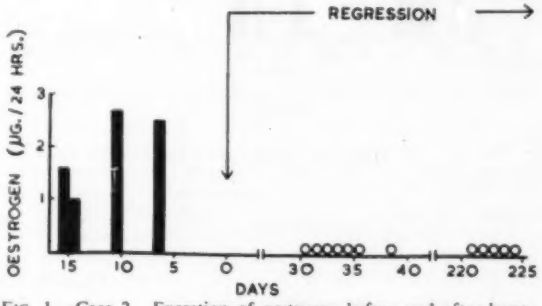

FIG. 1.—Case 2. Excretion of oestrogen before and after hypophysectomy. In Figs. 1–4 the day of operation is marked with a vertical arrow; oestrogen excretion is shown as total oestrogen—the sum of the oestrone, oestradiol-17β, and oestriol values. Each vertical column gives the mean of a duplicate determination on a 24-hour specimen of urine. Open circles on the abscissa indicate no detectable oestrogen.

aged 55, she was three years post-menopausal. She had metastases in the lumbar spine, an ulcerated chest wall, and skin nodules in the neck. Oestrogen excretion was low compared with the mean level for post-menopausal women with breast cancer and was reduced in the first post-operative month to levels indistinguishable from zero. Growth regression followed hypophysectomy, and this has continued up to the time of writing, 15 months after operation. Follow-up specimens obtained 13 months after operation showed the continued absence of oestrogen in the urine. The

oestrogen excretion in this patient (Fig. 1) illustrates the expected effect of hypophysectomy in abolishing oestrogen excretion.

In five further cases (Nos. 1, 3, 4, 6, and 8) a similar unequivocal fall to zero in oestrogen excretion was found after the first post-operative month, accompanied by regression of the disease.

Case 4 (Fig. 2).—This patient, aged 65, was studied within two weeks of operation, and oestrogen was detectable in the urine in amounts greater than those found before operation. This increase in oestrogen was confirmed by biological assay. No oestrogen was detected three weeks after operation, and follow-up specimens at nine weeks and 14 months suggest that the fall to zero continued. Skin and glandular metastases decreased after operation, and remission has been maintained up to the time of writing, 16 months after operation.

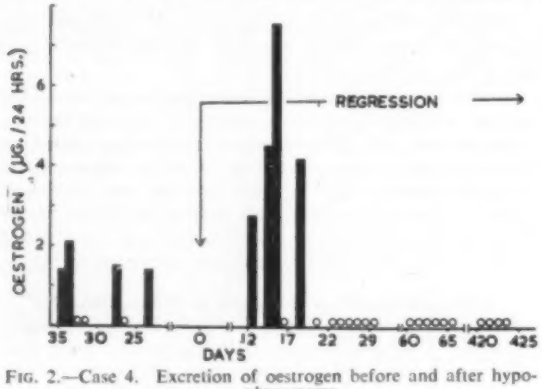

FIG. 2.—Case 4. Excretion of oestrogen before and after hypophysectomy.

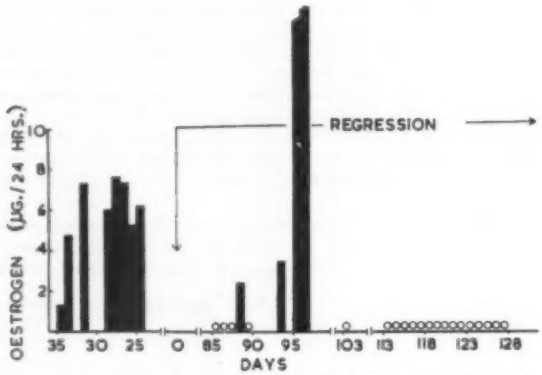

FIG. 3.—Case 5. Excretion of oestrogen before and after hypophysectomy.

Case 5 (Fig. 3).—In this patient, aged 42, an initial fall of oestrogen excretion to zero was associated with regression of cutaneous and skeletal lesions. Although this marked regression continued, oestrogen was detected in the urine for a short period some three months after operation. Biochemical estimations of urinary oestrogens, confirmed by biological assay, showed that the predominant urinary steroid was oestriol with trace amounts of oestrone. The total amount of oestrogen was equivalent to that found in normal menstruating women, and eight times the mean pre-operative level. In this case it would seem that regression of the disease following hypophysectomy is not invariably accompanied by a persistent fall in oestrogen excretion to zero.

Case 7.—This patient, aged 44, showed little fall in total oestrogen after hypophysectomy with remission of the disease : oestrogen was detectable in three of six specimens collected after operation.

Case 9.—In this patient, aged 40, hypophysectomy was accompanied by a remission of skeletal metastases, and this has continued to the time of writing, 15 months after operation, in the absence of detectable oestrogen. Hypophysectomy in this patient reduced oestrogen excretion to levels indistinguishable from zero by the chemical method used, but oestrogen was detectable on one occasion, one month after operation, by the more sensitive biological assay.

Two patients were studied with progressive disease after a previous oophorectomy and adrenalectomy. Case 10 had not benefited from this treatment, while Case 11 had been in regression for two years before exacerbation of breast and skin symptoms occurred. Oestrogen was not detectable either before or after operation, which was followed by remission of symptoms for three months in both cases. The disease thereafter progressed in Case 10, death taking place four months after operation. In Case 11, however, mastectomy had not been performed and the patient was still in regression up to the time of death from an acute bacterial infection following post-operative necrosis in both the involved breasts.

Mastectomy had not been performed in Case 1 and a marked regression of growth of the breast tumour accompanied a fall in oestrogen excretion at hypophysectomy. This

TABLE I.—*Oestrogen Excretion by Patients in Objective Remission after Hypophysectomy**

Case No.	Age	Pre-Hypophysectomy					Post-Hypophysectomy							
		Mean Oestrogen, µg. 24 hrs.				No. of Analyses	Mean Oestrogen, µg. 24 hrs.				No. of Analyses	Months After Operation	Period of Regression (Months)	Survival Time in Months
		O	D	T	Total		O	D	T	Total				
No Previous Endocrine Surgery														
1†	58	1·3	1·0	2·3	4·6	9	0·0	0·0	0·0	0·0	6	1	2	2
2	55	0·9	0·0	1·1	2·0	4	0·0	0·0	0·0	0·0	5	1	15	
							0·0	0·0	0·0	0·0	5	13		
3	61	1·9	0·4	2·5	4·8	10	0·0	0·0	0·0	0·0	4	1	10	12
4	65	0·9	0·0	0·0	0·9	7	1·3	0·7	1·5	3·5	6	½		
							0·0	0·0	0·0	0·0	16	1–14	16	
5	42	2·1	0·7	3·2	6·0	8	0·0	0·0	0·0	0·0	7			
							3·3	0·0	48·3	51·6	2	3	6	
							0·0	0·0	0·0	0·0	7			
Previous Oophorectomy														
6	50	1·6	0·6	1·0	3·2	24	0·0	0·0	0·0	0·0	1	2	5	6
7	44	0·9	0·3	5·7	6·9	10	0·8	0·0	4·0	4·8	6	1	4	5
8	49	1·0	0·6	3·0	4·6	2	0·0	0·0	0·0	0·0	13	1–8	11	
9	40	1·6	0·6	0·0	2·2	5	0·25	0·0	0·0	0·25	5	1		
							0·0	0·0	0·0	0·0	9	3–13	15	
Previous Oophorectomy and Adrenalectomy														
10	46	0·0	0·0	0·0	0·0	9	0·0	0·0	0·0	0·0	10	1	3	4
11*	48	0·0	0·0	0·0	0·0	5	0·0	0·0	0·0	0·0	6	1	3	3

*Age = That at hypophysectomy. O = Oestrone. D = Oestradiol-17β. T = Oestriol. In Cases 4, 5, and 9 post-hypophysectomy oestrogen excretion was confirmed by parallel biological assay. † Not previously mastectomized.

regression continued up to the time of death three months after operation. As in Case 11, post-mortem examination showed gross necrosis of the mass in the involved breast, and it is not improbable that death was caused by the liberation of toxins from rapid autolysis of necrotic tumour tissue.

The anticipated effect of hypophysectomy is to reduce and abolish oestrogen excretion. The overall results in this section confirm that this is generally true for women after the menopause or those who are in remission after oophorectomy. In seven of the nine patients no oestrogen could be detected after the first post-operative month, and the effect appears to be persistent. In two cases no oestrogen could be detected before operation, and oestrogen analyses, although zero after operation, provided no evidence of the completeness of the removal of the pituitary in these cases. However, in 2 of the 11 patients oestrogen was detected although remission of the disease followed operation.

If the pre-operative levels of oestrogen are considered the mean total oestrogen for the nine patients is somewhat lower than the mean level found for 39 women with metastatic breast cancer after the natural menopause or bilateral oophorectomy.

Oestrogen Excretion in Patients not Benefited by Hypophysectomy

Four women were studied in this group (Table II). All had previously been treated by mastectomy; three had undergone subsequent oophorectomy; the fourth had not menstruated for a year following a course of testosterone treatment. At the time of operation all patients showed evidence of progressive skeletal metastases, and these were unaffected by hypophysectomy. The average survival time after operation was eight months. In no case was oestrogen excretion reduced or abolished by operation. A typical example of the variation in amount and pattern of excretion is shown in Fig. 4 (Case 12). The mean level of oestrogen before operation of these four patients appears to be greater that the mean pre-operative level of the patients recorded in Table I obtaining benefit from hypophysectomy.

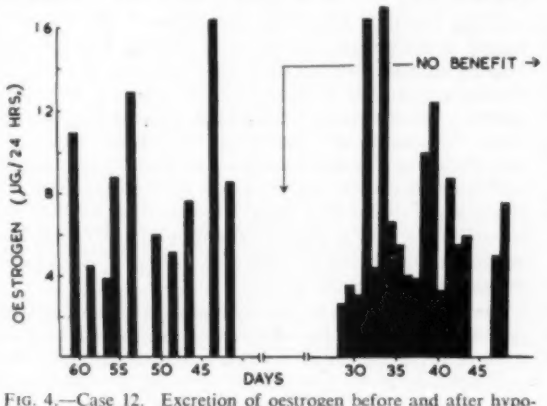

FIG. 4.—Case 12. Excretion of oestrogen before and after hypophysectomy.

Of incidental interest is the fact that Case 16 was a male suffering from breast cancer with widespread metastases. Neither orchidectomy nor subsequent hypophysectomy altered the progress of the disease. The latter operation reduced but did not entirely abolish oestrogen excretion.

Discussion

The object of this study was to decide if the excretion of oestrogen was correlated with the pre- and post-operative clinical state of patients suffering from metastatic breast cancer and subjected to hypophysectomy. Although the series is small, a correlation seems clearly established, since oestrogen excretion was generally absent in urine from patients in regression after hypophysectomy and present when the operation failed to benefit the patient. In four cases in remission oestrogen was demonstrated in the urine, but this was a transitory phenomenon in three of these patients. For example, Case 4 (Table I) was excreting more oestrogen two weeks after operation than before. This patient was studied at an earlier stage after hypophysectomy than the remaining cases. The presence of oestrogen 12 to 18 days after operation, followed by a period of 14 months in which no oestrogen could be detected, suggests that it may take two weeks for the elimination of circulating pituitary and adrenal hormones.

The amounts of oestrogen detected only by biological assay in Case 9 suggest that the grouping of patients in regression showing no oestrogen excretion by the chemical method may be an arbitrary classification depending only upon the sensitivity of the chemical method. No oestrogen could be detected in the urine of Case 5 for a long period. Three months after operation relatively large amounts of oestrogens were excreted for two days; this was followed by a prolonged period when again no oestrogen could be found in the urine. In both instances the chemical results were confirmed quantitatively by biological assay. We have no satisfactory explanation for this result, but it is extremely unlikely that the oestrogen could have been derived from the diet, since a patient after adrenalectomy in the same ward and on an identical diet excreted no oestrogen during this period.

In only one patient (Case 7) did oestrogen excretion continue on the same level as before operation, and this patient had an objective regression. It may be significant that survival time and the period of regression were short. This finding is discussed later.

The first two sections in Table I show that the mean pre-operative levels for the post-menopausal and post-oophorectomy patients obtaining benefit from hypophysectomy tend to be below the mean level found for women with cancer of the breast in these categories (Bulbrook *et al.*, 1958a). The mean levels were 3.6 and 4.2 µg./24 hours (total oestrogen) respectively, compared with 5 to 6 µg./24 hours. On the other hand, the mean amount of

TABLE II.—*Oestrogen Excretion by Patients Deriving no Benefit from Hypophysectomy*

Case No.	Age	Pre-Hypophysectomy					Post-Hypophysectomy						
		Mean Oestrogen µg./24 hrs.				No. of Analyses	Mean Oestrogen µg./24 hrs.				No. of Analyses	Months After Operation	Length of Survival in Months
		O	D	T	Total		O	D	T	Total			
Previous Testosterone Treatment													
12	41	1·9	1·6	4·9	8·4	10	1·5	1·3	3·9	6·7	19	1–2	4
Previous Oophorectomy													
13	41	2·9	1·2	4·9	9·0	10	1·6	2·9	2·4	6·9	9	1	7
14	49	1·9	0·4	0·0	2·3	3	0·8	2·3	7·1	10·2	13	1	9
15	46	0·8	1·8	5·6	8·2	7	0·3	0·3	11·0	11·6	8	1	7
Male Patient with Breast Cancer—Previous Orchidectomy													
16	59	0·4	0·3	7·7	8·4	11	1·1	0·6	0·0	1·7	4	2	8

All patients had previously undergone mastectomy. Age = That at hypophysectomy. O = Oestrone. D = Oestradiol-17β. T = Oestriol.

oestrogen excreted by the four patients who failed to benefit from operation (Table II) was 7 μg./24 hours—a value slightly higher than the mean level for all patients in this category, and higher than the mean pre-operative level of patients obtaining remission at hypophysectomy (Table I). There are not enough patients in the series for these findings to have any statistical significance, but there may be a tendency for patients with a low pre-operative oestrogen level to benefit from hypophysectomy while those with a high level do not. Further work is needed to check the validity of this suggestion.

In two instances patients who had been previously treated by oophorectomy and adrenalectomy were subjected to hypophysectomy. In neither case was oestrogen detected in the urine either before or after hypophysectomy, yet in both patients their objective regressions were short. Unless they were excreting amounts of oestrogen not detectable by the chemical method, these results suggest a direct participation of pituitary hormones in the maintenance of human breast cancer, as opposed to an indirect trophic effect on target organs. Similarly, in the patient already referred to (Case 7) objective regression occurred in spite of continued oestrogen excretion. Again, this result is explicable on the assumption that the levels of growth hormone, prolactin, or both had been reduced below a critical level.

In the four patients referred to in Table II the most simple explanation for the failure of hypophysectomy to influence the growth of the breast cancer is the continued excretion of oestrogens due to incomplete hypophysectomy. We have, as yet, been unable to study the transition from remission to relapse in this series. However, Hortling *et al.* (1957), using the vaginal-smear technique, found that oestrogen secretion increased simultaneously with the deterioration of the patient's clinical condition.

The explanation of failure or success following endocrine ablation for breast cancer must be largely speculative until we are able to assess directly the functional capacity of the human hypophysis with a reasonable degree of precision. The results of the investigations on the small number of patients in the present series suggest that repeated biochemical estimation of oestrogens before hypophysectomy may prove to be of some value in forecasting the clinical outcome of this operation.

Continued post-operative excretion of oestrogen, by indicating incomplete removal, suggests that no significant clinical palliation is likely to occur, while cessation of oestrogen excretion would suggest the reverse. The exceptions to these generalizations provide cogent reasons for supposing that the growth of some human breast cancers is maintained by the direct action on the tumour cells of anterior pituitary hormones.

Summary

The effect of hypophysectomy on the clinical state and on oestrogen excretion has been studied in 15 women and one man with metastatic breast cancer.

Patients obtaining regression following hypophysectomy tended to have a low pre-operative level of urinary oestrogen, and in the majority oestrogen excretion virtually ceased after operation. On the other hand, continued oestrogen excretion was not always exclusive of objective regression.

Patients deriving no benefit from operation tended to have a high pre-operative oestrogen excretion and continued to excrete oestrogen after operation.

We are grateful to the surgical staff and the staff of the radiotherapy department of St. Bartholomew's Hospital for allowing us to investigate patients under their care. We would like particularly to thank Professor Sir James Paterson Ross and Dr. A. A. G. Flemming. All the operations for hypophysectomy were performed by Mr. J. E. A. O'Connell, and we are grateful to him for allowing us to continue the observations on these patients.

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A BIOCHEMICAL CONCEPT OF TUMOUR GROWTH, INFILTRATION, AND CACHEXIA

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Among the many perplexing properties of a growing tumour is its ability to build up protein and increase in weight in a host (experimental animal or man) which is fast losing weight. This ability to obtain the precursors of its protein from the metabolic pool at the expense and to the detriment of the host has been investigated in some detail by Mider, Tesluk, and Morton (1948) (see Greenstein, 1954), and from the results they obtained with the transplantable Walker 256 tumour in growing rats they have been able to show three distinct phases in the growth history of the tumour and tumour-bearing animal. During the first stage (while the tumour is relatively small) both the tumour and the host gain weight. In the second stage the tumour alone continues to gain weight, and at an increasing rate. The host tissues in this second stage at first fail to gain weight and later may even lose weight. In the third and terminal stage (often very brief) the rate of growth of the tumour falls, and eventually the tumour itself may lose weight, although not as markedly as that of the rapidly wasting tissues of the host.

Such observations in the experimental animal, and the well-known clinical fact that tumours continue to grow even in cachectic subjects, suggest that the tumour is an autonomous entity capable of thriving irrespective of the metabolic status of the tissues of the host. It is obvious, however, that even the most autonomous neoplasm must have an adequate supply of metabolites for the purposes of growth, and if the essential metabolites are not forthcoming then the rate of growth must suffer.

The effect of dietary restriction on the incidence and rate of growth of spontaneous tumours has been the subject of much careful study. Tannenbaum and his colleagues (see review, Tannenbaum, 1947), in a series of brilliant experiments, have shown that dietetic restriction can greatly reduce the incidence of both naturally occurring and carcinogen-induced tumours in experimental animals. Indeed, some 14 different tumours have been shown to be affected in this manner, and the statistical evidence from insurance companies' records collected by L. T. Dublin in 1927 (quoted by Tannenbaum, 1947) shows that the incidence of various neo-

plasms is higher in overweight humans than in underweight ones. The growth of established tumours is not as dramatically affected by dietetic restriction as is tumour incidence, but nevertheless the rate of growth is dependent upon the nutritional status of the host (Rous, 1914; Tannenbaum, 1947; Ghadially and Wiseman, 1956).

From a consideration of these fundamental studies emerges the concept of a contest between the host and the tumour for the capture of metabolites circulating in the blood and in the extracellular fluid. Although such antagonistic behaviour between tissues in an animal has been suggested for a long time, and superior ability credited to the tumour cell, detailed experimental evidence has only recently become available to indicate an aspect of the nature of the metabolic mechanism which gives the tumour cell an advantage over normal host tissues.

It seems to us that, from a consideration of the work of many investigators, the metabolic superiority of the tumour cell is largely due to its enhanced amino-acid concentrating power. It is the purpose of this paper to evolve a hypothesis to show how infiltration of normal tissues by neoplastic cells, tumour anorexia, tumour cachexia, and the paradoxical growth of tumours in a wasting host can be explained on this simple biochemical basis.

Nature of the Metabolic Competition

Undoubtedly one of the most important factors in the successful synthesis of protein, and hence tissue growth, is the availability of the essential amino-acids for this purpose. Once the extracellular fluid in which the cells live becomes rich in these amino-acids (via the blood stream or autolysis of cells) then the next important step is the uptake of the amino-acids by the cells concerned. In any multicellular tissue we must picture the cells which share a common volume of extracellular fluid as competing with each other for the available metabolites. The cells which are better endowed in regard to the mechanisms concerned for metabolite uptake are in a better position for synthesis of new protein.

In 1913 Van Slyke was able to demonstrate that the intact cells of the animal body are able to accumulate amino-acids from the extracellular fluid and that they can concentrate the amino-acids until their content of these substances is about 10 times that of the animal's plasma. Since that time many tissues of the normal animals have been shown to concentrate amino-acids actively, and recently such work has been extended to neoplastic cells. In 1948 Christensen, Streicher, and Elbinger found that glycine, and probably alanine, serine, proline, methionine, and histidine, are actively taken up (that is, against a concentration gradient) by normal liver and muscle in the intact rat. Sassenrath and Greenberg (1954) and Greenberg and Sassenrath (1955) have published results of experiments in which they estimated, by specific microbiological means, 18 free amino-acids in the livers, muscles, and plasma of fed and fasting tumour-bearing rats, and they showed that the amino-acids were all present in higher concentration in the liver and muscle cells than in the plasma. It is a pity that these latter workers did not estimate the concentration of the free amino-acids in the tumours that their animals possessed.

Work with isolated normal diaphragm by Christensen and Streicher (1949) showed that the muscle could concentrate free glycine *in vitro*. In 1953 Wiseman found that the isolated small intestine of the rat was able to concentrate the L-forms ("naturally" occurring) of alanine, phenylalanine, histidine, methionine, and isoleucine. He showed (Wiseman, 1955, 1956) that isolated small intestine of the hamster was able to concentrate 13 different amino-acids and also that they competed with each other for the concentrating mechanism of the cell. While this work with normal tissue was being done, work with neoplastic cells was being carried out. In 1952 Christensen and Riggs found that the Ehrlich mouse ascites tumour cells actively concentrated amino-acids, and Christensen and Henderson (1952) showed that in the intact animal glycine, and possibly alanine, are concentrated by the Ehrlich ascites cells to a greater extent than by the liver. In 1955 Wiseman and Ghadially showed that suspensions of RD_3 sarcoma cells *in vitro* could actively concentrate histidine, proline, ornithine, lysine, and methionine. The results of our experiments indicated a qualitative difference in the capture of amino-acids by the sarcoma cells and normal intestine, in so far as the neoplastic cells could actively concentrate the diamino-acids, lysine and ornithine, while the intestine could not.

We were also able to show that apart from this qualitative difference there were two quantitative differences. Under similar conditions the sarcoma cells not only concentrated the amino-acids to a greater extent but the effect of methionine as an inhibitor of amino-acid uptake by cells was less marked. In the case of isolated normal intestine it was found that when methionine was present with an accompanying amino-acid in equimolecular amounts the methionine completely prevented the accompanying amino-acid from being concentrated. The effect of methionine on the isolated sarcoma cells, however, was only to depress, but not to abolish, the concentrative uptake of the second amino-acid.

Various earlier workers (Pilsum and Berg, 1950; Graham, Hier, Waitkoff, Saper, Bibler, and Pentz, 1950; Wretlind and Rose, 1950) have noted that excess dietary methionine retards the growth of young rats, and the results obtained by Wiseman (1955) show that this growth retardation is probably due to the powerful inhibitory effect of excess methionine on the uptake of other amino-acids by normal tissues. A consideration of the differences of the action of methionine on isolated intestine and sarcoma cells (Wiseman and Ghadially, 1955) led to the conclusion that excess dietary methionine should increase the rate of growth of a tumour in a tumour-bearing animal while at the same time causing the host tissues to waste. This, in fact, was shown to be the case (Ghadially and Wiseman, 1956) when 4% DL-methionine was added to the diet of rats bearing RD_3 sarcoma. The results of those experiments strongly suggested that the excess methionine decreased the ability of the normal tissues to take up other amino-acids and thereby provided a readier source of amino-acids for the growing tumour, whose amino-acid uptake was not so greatly affected by the excess methionine. Thus there was confirmation *in vivo* of the earlier *in vitro* findings.

Metabolic Superiority of the Neoplastic Cell

Numerous other experiments have also demonstrated this metabolic superiority of the neoplastic cell over its normal counterpart. Zamecnik, Frantz, Loftfield, and Stephenson (1948) found that slices of rat hepatomata (induced by the use of 4-dimethylaminoazobenzene) incorporated more radioactivity from labelled alanine and glycine than did slices of normal rat liver. Rutman, Cantarow, and Paschkis (1954) have shown that mitochondria from preneoplastic livers and from hepatomata of acetoaminofluorine-treated mice showed an enhanced ability (20 to 50% increase) in incorporating alanine-1-^{14}C into peptide linkages. Studies by Burke and Miller (1956) revealed that in the preneoplastic phase during 3'-methyl-4-dimethylaminoazobenzene carcinogenesis the livers of rats incorporated into proteins between two and three times the normal amounts of L-lysine. This was associated with a depression of katabolism of the amino-acid as evidenced by a yield of $^{14}CO_2$ from the labelled lysine lower than expected, and a decreased urea production. Tumours other than hepatomata show an increased uptake of radioactive amino-acids.

Zamecnik *et al.* (1948) and Winnick (1950) found that the rate of uptake of ^{14}C-labelled glycine and alanine into mouse mammary tumour homogenate was several times as great as that of normal mouse liver homogenate. LePage (1953)

has been able to demonstrate that the Gardner lymphosarcoma cells and the Ehrlich carcinoma cells can incorporate up to 50 times as much glycine-2-^{14}C into protein as can normal mouse liver cells. Mouse mammary tumour mitochondria show essentially the same phenomenon (Winnick, 1950). Roberts and Tishkoff (1949) have found that the preneoplastic epidermis of mice receiving applications of methylcholanthrene can concentrate free amino-acids to a greater extent than normal mouse epidermis. It would seem, therefore, that the ability to outdo normal tissues in the capture of amino-acids is an early acquisition of the neoplastic cell, and this we would expect if the neoplastic cell is to compete rapidly and successfully for these essential metabolites.

The rapid rate of incorporation of amino-acids into cellular protein in the neoplastic and preneoplastic cell, as compared with its normal counterpart, would keep the level of free intracellular amino-acid lower than it might otherwise be and thereby help the movement of more amino-acid into the cell from the extracellular fluid. Thus not only is the rate of production of neoplastic tissue kept high, but also the field is set for the continued deprivation of the local normal cells of adequate amounts of the precursors of their protein. An added advantage occurs in the event of the neoplastic cell being able to concentrate an essential amino-acid actively while the local normal cells are unable to do so. Under these conditions the local normal cells would be largely deprived of one or more essential amino-acids, and they would then virtually cease to produce their own intracellular protein, as all the precursors of a protein molecule must be present at the same time for protein synthesis. In the absence of one or more essential amino-acids, cells are unable to retain for any length of time those amino-acids which are available, and a negative nitrogen balance occurs (Cannon, 1948).

Activity of in vitro Preparations

We must point out at this stage that the enhanced activity of many of the *in vitro* preparations to incorporate labelled amino-acids into protein has not always been demonstrable *in vivo* (Griffin, Bloom, Cunningham, Teresi, and Luck, 1950; Kit and Greenberg, 1951; Tyner, Heidelberger, and LePage, 1952). It seems likely, however (Zamecnik, Loftfield, Stephenson, and Steele, 1951), that this is a result of inherent technical limitations, for it was observed that, although the avascular portions of the tumours were relatively inactive, the regions with a good blood supply showed high activity. From these observations we may conclude that the rate of uptake found in the *in vivo* experiments indicates only the average activity of the whole tumour and not the true activity of its most rapidly growing periphery. A similar view is put forward by Caspersson and Santesson (1942), and by Rutman *et al.* (1954).

It might be argued that the increased rate of incorporation of amino-acids into cellular and mitochondrial protein does not indicate that new and extra protein is being produced and that the results obtained by many of the above experiments might be the result of exchange of an amino-acid for another molecule of the same amino-acid without new protein synthesis occurring. However, the ability of the neoplastic cells to capture and concentrate free amino-acids at a rate higher than that of normal cells has been clearly demonstrated, and when that fact is added to the well-known observation that tumour tissues grow at a rate far greater than the host tissues it seems that the most likely explanation is that the tumour cells do in fact incorporate amino-acids into protein more rapidly than their normal counterparts.

An enhanced power to capture amino-acids is, of course, seen in fast-growing tissues other than malignant tumours—for example, placental tissue (Christensen and Streicher, 1948). The malignant tumour cannot, therefore, be looked upon as being unique in this respect; furthermore, it must be emphasized that an increased ability to capture amino-acids cannot be regarded as the hall-mark of malignancy or the essential neoplastic change. However, once this fundamental metabolic superiority is possessed by a tissue it has a potentiality to grow at the expense of its neighbours and will in fact do so whenever other growth-restraining influences fail to act. The understanding of this metabolic superiority enables many of the perplexing paradoxes of tumour–host relationships to be explained. It is, of course, possible that other important biochemical factors are involved at various stages in the neoplastic disease. Among such possible factors are competition for metabolites other than amino-acids, the production of toxic materials by established tumours, and changes in energy requirements.

Infiltration

The capacity of malignant cells to infiltrate into and destroy normal tissues is well known. One of the most recent and intriguing accounts attempting to explain the essential malignant change and the ability of neoplastic cells to wander is Green's (1954) antigenic theory of cancer. According to this hypothesis the ability of the malignant cell to wander and infiltrate is due to the failure of the antigenic mechanism of the body to "recognize" the cell once it has lost certain marker antigens. The growth of cells in unusual places and their extension beyond normal planes will therefore go unnoticed by the controlling mechanisms of the body. Loss of a series of such marker antigens, one by one, will confer an increasing independence upon a cell, and eventually such a cell will have the potential to infiltrate local tissues and spread beyond the normal physiological boundaries without arousing an adequate defence reaction on the part of a host. The development by a cell of the attribute to wander, however, seems to be in itself insufficient to account for its continuous growth unless such potentiality were aided by some metabolic superiority. Exploitation of its newly acquired growth independence, however acquired, must ultimately depend on its ability to outdo the local cells in a contest for available metabolites.

Infiltration by neoplastic cells does not only imply their growing between normal cells or along paths of least physical resistance, but it is essentially and ultimately a cell-by-cell destruction of the normal at the interface of the tumour and the normal tissue. In cases of low malignancy—that is, without marked metabolic superiority—there may be merely compression of neighbouring tissues and little real infiltration, but with highly malignant growths with overwhelming metabolic superiority it is not long before the normal cells are replaced by tumour tissue. Over a fairly broad zone surrounding a tumour one can as a rule detect islands of cells in various stages of disintegration, atrophy, and necrosis. Pressure exerted by the increasing tumour mass is usually the explanation given to account for the death of the normal cells at the tumour's advancing edge, but cannot in fact be the explanation (as already pointed out by Ghadially and Wiseman, 1957). The growing edge of the tumour derives its blood supply from vessels at the tumour/normal tissue interface (Algire and Chalkley, 1945), and any appreciable rise in pressure at this region would destroy the tumour cells as well as the normal cells.

It seems to us that the phenomenon of infiltration by a cell which has lost its marker antigens can best be explained on the basis of a metabolic competition of the type described in the early part of this paper. The advancing columns of tumour cells are bathed in the same extracellular fluid and share the same local environment as the adjacent normal cells. Thus it is inevitable that a local competition for available amino-acids will arise. The more efficient power of concentration possessed by the tumour will have a two-fold action. Firstly, it provides the tumour with material necessary for protein synthesis and growth, and, secondly, it deprives the adjacent normal cells of their basic metabolic requirements and thereby induces atrophy, degenerative changes, and finally necrosis. It is for this reason, in our opinion, that the normal cells at the periphery of a growing tumour suffer most. The disintegrating normal cell no doubt provides further metabolites for the insatiable

demands of the flourishing tumour. Thus our hypothesis explains not only why malignant cells flourish and infiltrate but also why the normal cells are destroyed.

Anorexia and Cachexia

As previously mentioned, three phases have been identified in the growth history of the tumour and the tumour-bearing animal. In the first stage the volume of tumour tissue is small and the needs of both the normal and the neoplastic cells are easily met from the general metabolic pool. By the time that the second stage is reached, however, the volume of tumour tissue has increased, and it is at this stage that the severe competition for essential amino-acids must arise. The tumour, by virtue of its more powerful amino-acid concentrating mechanism, deviates large amounts of the available amino-acids for its own protein synthesis, and the normal tissues begin to suffer as the metabolic pool is heavily depleted. The katabolic processes in normal tissues continue (perhaps at an increased rate), but the amino-acids for the anabolic process are no longer freely available.

One of the tissues to suffer early on in this metabolic competition is the intestine, and as a result food intake is reduced. The intestine of a tumour-bearing host is found to suffer a severe weight loss in common with most other normal tissues (Bloor and Haven, 1955), and in rats bearing a Walker carcinoma 256 the intestinal weight may be reduced to about three-quarters of that in control animals. Herein probably lies a good deal of the explanation of the anorexia seen both in patients and in experimental animals suffering from neoplastic diseases. The rate of turnover of cells in the intestinal mucosa has been demonstrated to be very rapid indeed, and the entire mucosa is replaced every 1½ days in the rat (Leblond and Stevens, 1948) and every 2½ days in the cat (McMinn, 1954). This rate of tissue production entails much protein synthesis and calls for a constant supply of amino-acids from the general metabolic pool. Such a demand on the metabolic pool will tend to become more onerous in the later stages of neoplastic disease, and when scarcity of essential metabolites begins to make itself felt the tumour will continue to grow at the expense of the intestine as well as of other normal tissues.

Increasing anorexia and cachexia then herald the third and terminal stage of the disease, for not only is the metabolic pool being rapidly drained of amino-acids by the tumour, but in addition the intestine is no longer able to replenish that pool from the diet efficiently.

As well as obtaining amino-acids in large amounts from the extracellular fluids of the body, there is an actual translocation of amino-acids from normal to neoplastic cells. The work of White (1945) showed that mouse mammary carcinoma continued to grow even when the diet contained almost no nitrogenous substances. Much of the amino-acids necessary for the growth of the mammary tumour could have come from no other source except the normal tissues.

In contrast to other normal tissues, the effect of the growing tumour on the liver is more complex. Instead of the wasting as seen in most other normal tissues there is often an actual gain in liver weight during the earlier stages of the disease (Medigreceanu, 1910; Cramer and Lochhead, 1913; McEwan and Haven, 1941; Yeakel, 1948), and Abels, Rekers, Binkley, Pack, and Rhoads (1942) found that there was liver hypertrophy in 42% of patients suffering from gastro-intestinal cancer. The increase in weight of the liver is due to an increase in liver nitrogen (Yeakel, 1948; Sherman, Morton, and Mider, 1950) as well as an increase in liver water content (McEwen and Haven, 1941). It has been suggested that some growth-promoting factor is produced by the growing tumour and acts specifically on the liver (Paschkis, Cantarow, Stasney, and Hobbs, 1955).

The liver hyperplasia may, on the other hand, be due to an increased liver activity concomitant with the increasing metabolism of the growing tumour, and may be similar to the liver enlargement seen in pregnancy (Cramer and Lochhead, 1913; Walter and Addis, 1939; Poo, Lew, Lee, and Addis, 1940). The stimulating effect on the liver of a growing transplanted tumour has also been shown by Annau, Manginelli, and Roth (1951) and by Malmgren (1956). The latter was able to demonstrate an increase in the number of mitoses in the liver, and similar changes in liver mitosis were observed after the administration of saline extracts of tumours (Malmgren, 1956). But eventually, in the third stage of the disease, when most of the normal tissues are rapidly losing weight and even the rate of growth of the tumour is reduced, the liver suddenly shows a marked weight loss (McEwen and Haven, 1941). It appears that when the last usable sources of nitrogen from the normal tissues of the body have been utilized by the growing tumour mass the liver suddenly surrenders its own nitrogenous materials to keep the malignant cells supplied with metabolites. At this stage of the disease the derangement of the host's nitrogen metabolism has proceeded so far that death rapidly brings the whole process to an end.

Conclusion

The success of the neoplastic cell once it has appeared in the host seems to us to be in the superior ability of such cell to capture from the internal environment, and to concentrate intracellularly, the free amino-acids essential for its protein synthesis. In this activity the neoplastic cell is superior to the normal cell, and the degree of such superiority decides the eventual history of the tumour. Those tumours which are only slightly more active than the normal in their ability to concentrate amino-acids will grow slowly and produce only minor metabolic disturbances, while the more active ones will infiltrate faster, cause anorexia, and produce rapid cachexia and eventual death.

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MONKEY-BITE ENCEPHALOMYELITIS

REPORT OF A CASE—WITH RECOVERY

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Those who handle monkeys are frequently bitten, usually without untoward results. Exceptionally, however, disaster may follow. Sabin and Wright (1934) first recorded a case of acute encephalomyelitis in a doctor who had sustained such a bite. Within three days vesiculo-pustular lesions developed at the site of the bite followed by regional lymphangitis and adenitis. A week later signs of motor and sensory disturbances began in the legs and bladder, and these were followed by an acute ascending myelitis. Death in respiratory failure occurred in a few days. From lesions in the cord, brain, and spleen a strongly neurotropic filterable virus was isolated which they named "monkey B." Sabin (1949) also reported a second case with a somewhat similar history, course, and termination, though there had been no bite and infection had presumably resulted from contamination of a laceration on the right hand with infected monkey saliva. A similar virus was again recovered.

Olitsky and Casals (1952) referred to two similar cases following monkey-bites; but they were not reported, but were presumed to be virus B infection; both showed encephalitis: both were bitten by monkeys prior to the disease; both, however, were not studied for virus isolation (Olitsky, 1958, personal communication). Sabin (1958, personal communication) believes that he has now traced 10 additional cases retrospectively, one of which recovered with severe disability. We have knowledge of one fatal case in this country, while two other fatal cases have been reported from Canada (*The Times*, March 22, 1958). How many of these have been studied virologically is unknown and none has been published. The following is the first complete account of the natural history of the disease, as well as the first recovery to be recorded. This is the more pertinent, since it is now clear that monkey-bite encephalomyelitis is not only a lethal but an increasing hazard.

(Virus B appears to be closely related to the herpes simplex virus of man, of which, indeed, it may be regarded as the simian variant. Most commonly it causes shallow ulceration on the dorsum of the tongue, though ulceration may occur elsewhere in the mouth or pharynx. Rarely it excites a vesiculo-pustular eruption on the lips. An important point is that the animal appears quite well, although at post-mortem examination the tracts of the cranial nerves may show multiple infiltrations by microglia surrounding cells containing what appear to be inclusion bodies. In tissue culture, virus B causes typical ballooning of the cells, frequently resulting in the formation of giant cells.)

Case Report

A monkey-handler aged 31 had been immunized against poliomyelitis in midsummer, 1957. On September 24 he was bitten in turn by two apparently healthy monkeys, once on the terminal phalanx of the left index finger and once on the dorsum of the third left finger. Both lesions were made to bleed and washed under the running tap, following which tincture of iodine was applied. They healed uneventfully. On September 30 he was vaccinated against influenza. On October 7 he went to his doctor complaining of a pain between the shoulder-blades, which the following day developed into a left-sided girdle pain and later passed off. (This was attributed to the vaccination against influenza.) For the next few days, apart from a headache, he felt well, but on October 13 his left leg gave way at work and he was sent home as a case of influenza. On the following day he could scarcely walk and was unable to pass water. He was sent to hospital as a suspected case of poliomyelitis.

When seen by one of us (G. E. B.) at Maidenhead Isolation Hospital on October 16 he was febrile but conscious and co-operative. He had been vomiting frequently. He could not sit up, but could bend his head freely—there was no true meningism. Pupillary reactions were normal, but there was marked anisocoria, with twitching of the face and trembling of the tongue. The abdominal reflexes were present. The left arm was weak and the triceps-jerk absent. The right arm appeared normal, but the reflexes were grossly exaggerated; the muscles of the back, pelvis, and abdomen were also weak; the left leg was almost immobile, with absent jerks; the right was weak and the reflexes were reduced; the plantars were equivocal. In addition there was loss of touch, pain, and vibration sense over the left lower leg and ankle, and a patchy loss of sensation over the lower half of the body generally. A lumbar puncture showed a clear fluid containing 75 cells per c.mm.; protein, 80 mg. per 100 ml.; sugar, 68 mg. per 100 ml. His was clearly not a case of poliomyelitis, and, in view of the history, the possibility of virus B infection had to be considered.

Two days later (October 18), because of developing weakness of respiration, he was transferred to the South Middlesex Hospital. On admission paralysis was found to have progressed. In addition to the signs previously noted there was weakness of the intercostals and of the left leaf of the diaphragm, and the vital capacity was down to 2 litres. The abdominal reflexes too were now absent. Both lower limbs were extremely weak, with absent reflexes, and the reflexes were also reduced in the left arm. The right arm still seemed normal, with increased jerks. There was now some left facial weakness, and, though the anisocoria had disappeared, there was marked nystagmus on looking upwards and to the right. Sensory loss over the lower half of the body was widespread and retention of urine was absolute. In the hope that it might contain some relevant antibody, he was given 10 ml. of human gamma-globulin.

On the morning of October 19 his vital capacity had fallen to 800 ml. and respirations were rapid and shallow. He was placed in a tank respirator and at first settled down well. High pyrexia continued, however, and vomiting was frequent. His vital capacity continued to fall—to 460 ml. at 8 p.m. At the same time his voice became hoarse, and pooling of secretions in the pharynx necessitated frequent suction. He was therefore removed from the tank respirator and, under general anaesthesia, a tracheostomy was made, a cuffed endotracheal tube was inserted, and he was placed on intermittent positive-pressure respiration, using a Radcliffe respirator. As the nose was impassable to a catheter, an intravenous drip was set up in which cortisone, 100 mg., was incorporated. A further 10 ml. of gamma-globulin was also given.

As is common in such cases, progress during the following week was somewhat chequered, though eventually the patient settled down fairly well. During the week, cortisone,

200 mg. daily, was administered by intramuscular injection, antibiotic cover being maintained. The temperature fell by slow lysis. Limb paralysis was now almost complete, with absent reflexes all round; facial weakness was notable and nystagmus pronounced. Fortunately, some improvement in swallowing soon began, so that by October 26 fluids could be taken by mouth and by October 29 semi-solids could be taken as well; intravenous maintenance was therefore discontinued. Shortly thereafter some increase in motor power in the limbs generally was noted, but painful involuntary spasms appeared in the left leg. On November 7 the patient went for two minutes without assistance to respiration, and breathing power continued to improve until November 9, when it was interrupted by massive collapse of the left lung which was cleared only by vigorous physiotherapy. Thereafter respiratory capacity increased slowly but steadily, and it was possible to substitute a rocking-bed for positive-pressure respiration for short periods. General progress was much influenced by an intractable bladder infection, at first with *E. coli* and later with *Pseudomonas pyocyanea* requiring treatment with polymyxin B. The pressure points also gave trouble, and an intractable bedsore developed over the sacrum which demanded the use of a ripple mattress. Daily enemata were also necessary. On November 8, for the first time, he felt an injection into the right buttock.

The patient's psychology presented a curious parallel to his physical condition. At first he was well controlled if occasionally confused, and he was always an unsatisfactory witness for sensory evaluation. When placed in the tank respirator he was fairly calm, but a few days later he became increasingly irritable, excitable, and emotional, often weeping spontaneously. Subsequently he stated that he had no memory of events from the time he was placed in the respirator on October 19 until about November 15. After that date, though still highly emotional, irritability diminished markedly, but he continued very apprehensive, thereby delaying his weaning from the respirator considerably. About November 15 bladder control became re-established. Gradual improvement in breathing resulting in a vital capacity of 2 litres enabled artificial respiration to be discontinued on December 9. About this time reflexes and sensation also began to appear in the limbs, and by January 15, 1958, power was regained almost fully in the right arm and leg and to a considerable extent in the left arm. The left leg, however, remained sharply contracted and tremulous and apt to go into painful clonic spasms on the least stimulation. On passive extension it gave a sensation reminiscent of that encountered in cases of post-encephalitis lethargica. The plantar reflexes remained extensor. By now the left facial nerve had quite recovered and the pupils were normal, but there was still some fine residual nystagmus, especially on looking upwards.

On January 27 the patient was transferred to a long-stay hospital for further rehabilitation. The latest report (April 9) stated that he was quite fit, and with elbow crutches and a full-length calliper could walk 25 yards without aid. The power in his arms was back to normal. There was no sensory disturbance left and bladder control had entirely returned. The spasm in the left leg was progressively diminishing and there was every indication that he would be able to resume an active life and return to full work in due course.

Comment

The picture is consistent with a virus infection which ascended along the peripheral nerves to the cord, producing widespread foci of inflammation throughout the whole central nervous system. It is remarkable that signs were much more pronounced and lasting on the left (the bitten side) than on the right, which recovered much more rapidly. Lesions appeared to affect the long tracts mainly, the anterior horn cells escaping undamaged. Sensory changes, while at one time widespread, also proved transitory.

Psychological changes were also notable—irritability and gross emotional lability. There was amnesia for a period of about three weeks. The patient's intelligence seemed to be unimpaired.

The value of the gamma-globulin and of the cortisone given in treatment is difficult to assess. Even if the former contained significant quantities of herpes simplex antibody valid against virus B, it would appear (by analogy with other virus disease) to have been given much too late to exert any appreciable influence on the course of the condition. From the time that cortisone was administered, the march of the paralysis appeared to halt and the temperature returned to normal by a slow lysis, but there was no dramatic fall such as is commonly seen in other conditions where it has proved effective.

A NOTE ON VIROLOGY

By W. Wood, O.B.E., M.B., B.S.

Attempts to isolate the causal agent from faecal and serum samples and determinations of virus B neutralizing antibody on acute and convalescent sera were carried out. All tests were run in monolayer tissue cultures of monkey-kidney tissue, employing a method outlined previously (Tyrrell, Keeble, and Wood, 1956). Samples of faeces were prepared for inoculation by making a 10% suspension in normal saline and clarifying by centrifugation at 2,500 r.p.m. Serum samples were titrated against two strains of virus B—one isolated at Sefton Park, the other isolated in Canada in 1953 (Wood and Shimada, 1954).

Specimens.—Faecal samples were obtained on October 16 and 28, 3 and 15 days respectively after onset of illness. Serum samples were obtained on October 16 and 21, Novem-8, and January 21; 3, 8, 26, and 100 days respectively after onset.

Results.—Tests for virus isolation on both faecal samples and the first three serum samples were negative. The final serum sample was not tested for presence of virus.

The virus B antibody titres in the four serum samples were as follows: day 3, 1:16; day 8, 1:25; day 26, 1:48; day 100, 1:32.

Conclusions.—Failure to isolate virus B from faecal samples is considered of no significance in that the route of infection via a wound would not necessarily involve alimentary infection. The results of the antibody tests are difficult to interpret, as we are ignorant of the degree to which neutralizing antibody develops in humans recovering from a virus B infection. It is also possible that the administration of cortisone in this patient depressed the antibody response in convalescence. However, a moderate rise in antibody did occur between the third and 20th days which, if considered in conjunction with the clinical data, suggests virus B encephalomyelitis as a probable diagnosis. It should be remembered, however, that monkeys may harbour many different viruses whose potentialities for causing disease in man are not yet fully known, so that it is not impossible that a virus of monkey origin other than virus B may have been responsible for this patient's disease.

Summary

A case of encephalomyelitis following monkey-bites is described. After a very stormy illness necessitating tracheotomy and intermittent positive-pressure respiration the patient made a good recovery and should be able to return to an active life.

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NEUROLOGICAL COMPLICATIONS OF PERTUSSIS IMMUNIZATION

BY

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Since Madsen (1933) first drew attention to the possibility of serious consequences following active immunization against whooping-cough, reports of neurological sequelae of such immunization have come from various parts of the world. These sequelae (post-inoculation poliomyelitis is not being considered here) have ranged from transient convulsions with complete recovery to gross crippling, mental retardation, and death.

A survey of the literature, greatly facilitated by Köng's (1953) review of cases reported up to 1951, revealed records of 107 cases. A further case is now reported (the seventh from Great Britain), together with a review of the literature.

Case Report

A male child was born at full term on September 28, 1954, weighing 5 lb. 13 oz. (2.635 kg.) following an uneventful pregnancy (apart from an attack of acute salpingitis at 11 weeks, associated with a negative Wassermann reaction and gonococcal complement-fixation test, which responded rapidly to chloramphenicol) and an uncomplicated labour. His parents and two elder brothers were normal, physically and mentally, and there was no family history of allergy, mental disorder, convulsions, or other neurological ailments.

No abnormalities were found in the neonatal period, apart from a minor degree of hypospadias not considered worth treating, and the child thrived from the outset.

Until May 25, 1955 (aged 8 months), progress was normal and he had had no illnesses. The mother, an intelligent woman, considered him more advanced than his normal brothers had been at the same stage, and the milestones of development were well in keeping with the criteria of normality enumerated by Illingworth (1953).

On May 25 he was given a first inoculation of 1 ml. of combined diphtheria–pertussis vaccine (containing a plain suspension of 20,000 million *Haemophilus pertussis* and 25 Lf of fluid diphtheria formol toxoid). That night he was whimpering and unsettled, an unusual feature for him. Early next morning he was drowsy, hypotonic, and pyrexial, and the following morning—that is, within 48 hours of the injection—convulsive episodes began, described by a doctor then attending him as "involving a preliminary cry which is not his usual sound, clutching at the chest, queer breathing, and spasms of all four limbs." Rolling of the eyes was also noted. The pyrexia settled that day, but the fits persisted (one to four daily) despite bromides. That day, too, the child was no longer sitting up, could not support his head, and was indifferent to his environment.

Because the fits and associated features persisted, he was admitted to hospital three weeks after the inoculation. Observation revealed a child without interest in anything, who, if placed in a sitting position, could remain thus unsupported for only a few seconds, and who was having bouts of fits, each lasting a few seconds and each bout a few minutes. Apart from these findings, physical examination revealed no abnormalities, and the blood count, cerebrospinal fluid, and urine examinations were normal. The Wassermann reaction and Mantoux (1/100) were negative. Several weeks later skull *x*-ray films and lumbar encephalography showed no abnormality apart from the left lateral ventricle appearing slightly larger than the right.

At 11 months of age the child was severely retarded mentally, and phenobarbitone, ¼ gr. (16 mg.) twice daily, was needed to control his fits.

At 15 months grand-mal episodes became associated with the original convulsive pattern, and it was found necessary to increase the dose of phenobarbitone to 1 gr. (65 mg.) daily, and introduce phenytoin sodium, ¼ gr. (50 mg.) thrice daily.

Electroencephalography on May 16, 1956 (aged 19½ months), was considered diagnostic of epilepsy with the epileptic activity generalized and no focus. The main activity was in the delta range and of high frequency.

At 2 years of age no significant progress had been made mentally; fits were controlled with phenobarbitone, 1 gr. (65 mg.) twice daily, and primidone, 250 mg. twice daily; and there were no focal neurological signs.

At 3 years the child remained grossly retarded mentally, with no speech or understanding of speech, inability to do anything for himself, and an I.Q. of 23 on the Griffiths mental development scale. Fits were less severe and were controlled with primidone, 250 mg. twice daily, alone. Localizing neurological signs were absent, as were signs of disease elsewhere.

In the accompanying review of the literature, the 107 case reports from 25 sources mentioned in Table I were examined.

TABLE I

Authors	No. of Cases	Source
Anderson and Morris (1950)	1	Britain
British Medical Journal (1949)	1	"
Brody (1947)	2	U.S.A.
Byers and Moll (1948)	15	"
Cohen *et al.* (1955)	2	"
Doull *et al.* (1936)	3	"
Escardo and Vazquez (1950)	1	Argentina
Globus and Kohn (1949)	2	U.S.A.
Grace (1950)	2	Canada
Halpern and Halpern (1955)	15	U.S.A.
Kendrick and Eldering (1939)	1	"
Köng (1953)	2	Switzerland
Laplane (1950)	1	France
Livingston (1954)	7	U.S.A.
Low (1955)	1	"
Madsen (1933)	2	Denmark
Miller and Stanton (1954)	2	Britain
Rambar *et al.* (1941)	1	U.S.A.
Sako *et al.* (1945)	2	"
Sutherland (1953)	1	Britain
Taylor (1938)	1	U.S.A.
Toomey (1949)	38	"
Tudor (1951)	1	"
Vahrman (1950)	1	Britain
Werne and Garrow (1946)	2	U.S.A.

General Data

Sex of Affected Children.—Byers and Moll (1948) thought that the difference in sex incidence in their cases was similar to that encountered in relation to other substances causing gross injury to the developing nervous system. In the 22 other instances where the sex of affected children is stated a similar, though less striking, difference is present (Table II).

TABLE II

	Males	Females	Total
Byers and Moll	12	3	15
Others	14	8	22

Age When Inoculated.—This varied from 4 days to 3 years, most inoculations being done between 6 and 15 months. These figures simply reflect the ages when immunization is usually carried out, and the only conclusion to be drawn from them is that neurological sequelae may occur at any age in which immunizations are done.

Vaccines Used.—The vaccine used is recorded in 68 instances: in 28 a pertussis vaccine was used alone; in 12 a combined diphtheria–pertussis vaccine; and in 28 a combined diphtheria–tetanus–pertussis vaccine. The vaccines were prepared in a variety of ways by different manufacturers, and included fluid, alum-precipitated, aluminium hydroxide adsorbed, and detoxified formalized preparations. In Byers and Moll's (1948) study of 15 cases alone, the products of eight different manufacturers were identified, and in

Toomey's (1949) series of 38 cases at least six different pharmaceutical laboratories were concerned.

No significance can be attached to the number of times when pertussis vaccines alone or combined vaccines were used. These merely reflect the trends in immunization practice and the nature of the material under review. Thus, in the 10 cases reported up to 1945, pertussis vaccine was used alone in all, and thereafter combined vaccines became implicated too because of their increasing use. Further, in the report of Halpern and Halpern (1955), for instance, a triple vaccine was implicated in all 15 cases simply because their questionary was concerned only with triple vaccine immunization.

It is generally agreed that the pertussis antigen in all these vaccines is responsible for the reported neurological sequelae. There are good grounds for this view. Thus, the clinical manifestations of neurological complications following injections of pertussis antigen alone and of combined antigens containing pertussis are so strikingly similar that a common factor in all these vaccines is very probable. That this factor is pertussis antigen is suggested by the observations of Miller and Stanton (1954) that neurological complications of pertussis vaccination "are different from those encountered in other prophylactic inoculations in that the illness is always cerebral" and that "the neurological sequelae of a particular prophylactic inoculation appear to be similar in distribution to the neurological complications of the infective disease concerned." Complications of whooping-cough include convulsions and upper-motor-neurone type paralyses (Banks, 1949), and Cockburn (1951) points out that the convulsions may be the precursors of mental deficiency in a small number of cases. This is precisely the sort of pattern observed in the cases under review, irrespective of whether pertussis antigen alone or combined vaccines containing pertussis antigen were used.

Dose of H. Pertussis in Vaccines Used.—In 28 instances the number of *H. pertussis* organisms in the injection followed by neurological complications is recorded. This ranged from 1.5 to 45 thousand millions with no particular tendency for reactions to be associated with larger doses (Table III).

TABLE III

Dose (in 1,000 millions of organisms) ..	1–15	16–30	31–45
No. of cases	8	12	8

Injection Associated with Reaction.—In 61 instances where the injection order is given, neurological sequelae occurred for the first time, as shown in Table IV. These figures indicate that a reaction may occur with any injection, and, possibly, a decreasing likelihood for subsequent injections to provoke reactions the more previous ones there have been that have not done so. In seven cases neurological sequelae followed more than one of the injections (the first

TABLE IV

Injection order	1st	2nd	3rd	4th
No. of cases with neurological sequelae ..	26	20	12	3

of these injections producing sequelae is recorded in Table IV). It is notable that only one of these seven children recovered rapidly and completely (a case of Grace's, 1950). Of the remaining six children, two died 24 hours (Low, 1955) and 7 weeks (Brody, 1947) respectively after the last inoculation, and four were left with sequelae ranging from recurrent convulsions to gross physical and mental deterioration (Brody, 1947; Byers and Moll, 1948)—this despite the fact that earlier inoculations had not been thought to have had consequences serious enough to contra-indicate subsequent ones.

Past Personal and Family Histories

An analysis of these data is difficult to interpret because in many instances no information is given, and when it is given the amount varies greatly from author to author.

TABLE V

	Personal History No. of Cases	Family History No. of Cases
Neurological abnormalities	7	6
Allergic manifestations	1	5
Normal	48	16
Not stated	51	80

Such an analysis is shown in Table V. It may be presumed that considerably more of the personal and family backgrounds were normal than is indicated by these figures, and this is often implied. Table V records only the instances where this was actually stated.

Clinical Features of Acute Illness

Time Interval Till Onset of Symptoms.—The early onset of neurological symptoms was characteristic, though not invariable. Table VI shows the time interval from inoculation to the onset of symptoms in the 63 instances in which it was recorded.

TABLE VI

Time interval in hours	Up to 12	13–24	25–36	37–48	49–72	Over 72
No. of cases	39	9	4	3	2	6

State of Consciousness.—In all instances where this is mentioned changes varying from listlessness to deep coma occurred.

Convulsions.—These, ranging from mild localized episodes to severe generalized ones, were an almost invariable and striking feature. There were, however, several notable exceptions: In one case reported by Brody (1947), four different inoculations (the last an intradermal one) between the ages of 6 and 41 months were associated with severe neurological sequelae at progressively shorter intervals, culminating in complete paralysis and death, apparently without associated convulsions; in Sutherland's (1953) case, listlessness and weakness of the limbs appeared some five to seven days after a third inoculation, with evidence of bilateral pyramidal-tract dysfunction about one month later, and apparent complete recovery within seven months, with no mention of convulsions; and in one of Miller and Stanton's (1954) cases neurological signs (drowsiness and right hemiplegia) were delayed for about a week after a third inoculation, with right hemiparesis still present two years later—here, too, convulsions are not mentioned.

Pareses or Paralyses.—These were specifically stated to have occurred in 19 cases.

Other Features.—Besides the above neurological signs, occasional cases presented additional features such as cyanosis, hiccups, diarrhoea, and vomiting. In 39 cases where the temperature is mentioned, it was elevated in 35. Pyrexia is, however, a not infrequent transient concomitant of immunization in which no question of neurological sequelae arises.

Mortality.—In 8 cases death was reported within 48 hours of inoculation, 7 of them within 24 hours.

Progress

Complete Recovery.—This was specifically reported in 41 cases, including 23 of Toomey's (1949) 38, and 11 of Halpern and Halpern's (1955) 15, and presumably occurred in at least nine other instances.

Persisting Morbidity.—Follow-up of the affected children for varying periods revealed evidence of persisting abnormality (Table VII). So far as could be determined from the case reports, in a number of cases in which absence of details makes a fuller analysis of the above signs somewhat hazardous, these signs were distributed as follows: A only, 9 cases; B only, 8; C only, 1; A+B, 2; A+C, 2; B+C, 3; A+B+C, 6. Thus a total of 31 children were specifically

TABLE VII

Major Signs	Follow-up Period	No. of Cases in Which Actually Reported
A = Recurring convulsions	2 months—5½ years	19
B = Pareses and paralyses *	1 month—3 years	19
C = Mental retardation	2 months—5½ years	12

* Varying from slight hem paresis to gross crippling.

reported as having physical and/or mental signs of cerebral involvement one month to five and a half years after immunization.

Mortality.—Fifteen deaths (seven of them within 24 hours) were reported at varying time intervals since inoculation (Table VIII). Thus, an analysis of the available data indicates a recovery rate of about 50%, a persisting

TABLE VIII

Time interval since inoculation	1–48 Hours	1–2 Months	6 Months	20 Months	Unspecified
No. of deaths	8	2	1	1	3

morbidity rate of about 30%, and a mortality rate of about 15%. The small percentage of cases unaccounted for because of lack of information in the reports would not significantly alter these figures.

Aetiological Considerations

Various hypotheses to account for the complications discussed have been advanced from time to time, but each is open to objection and there is still no unanimity of opinion. Among the suggested causes are the following.

1. *A Sensitization Phenomenon.*—Miller and Stanton (1954) considered that "most neurological illnesses which follow prophylactic inoculation are manifestations of hypersensitivity," and Brody (1947) favoured a sensitization phenomenon as an explanation in the two cases reported by him, pointing out that both had a family history of allergic disturbances. However, allergy was recorded in only two other instances in the reviewed cases: the father of twins reported by Werne and Garrow (1946) as having died within 20 hours of a second diphtheria–pertussis inoculation had had two episodes of angioneurotic oedema of the lip; and one of Köng's (1953) cases had a personal and family history of asthma and eczema. An antigen-antibody response to previous specific sensitization has been suggested as a possible cause, but this is difficult to reconcile with the relatively large number of children who developed neurological sequelae following a first inoculation. It could well account, however, for some of the other cases—for instance, those of Werne and Garrow (1946), where necropsies "disclosed lesions consistent with death in anaphylactic shock."

2. *A Specific Toxin or Toxins Produced by H. Pertussis.*—Toxins have been isolated from *H. pertussis* cultures (Byers and Moll, 1948); and Miller (1951), who favours this view of the aetiology, points out that they are known to be neurotropic in experimental animals. However, Byers and Moll (1948) have raised the serious objection that as these toxins are unstable they can hardly survive in properly aged vaccines.

3. *Some Constitutional Predisposition in Affected Children.*—The sex ratio in Byers and Moll's series has been thought to suggest this possibility (*British Medical Journal*, 1950), but it is difficult to know what is meant by the term "constitutional predisposition." Certainly a large proportion of the patients reviewed were regarded as normal in all respects prior to their inoculations.

4. *Pyrogens Contaminating Vaccines.*—While this hypothesis has sometimes been postulated, there appears to be no definite evidence in favour of it.

5. *Accidental Intravenous Injection of Vaccine.*—As Faber and Miller (1948) have pointed out, this could be a factor only in reactions occurring almost immediately after injection. In the reviewed cases, reactions within half an hour were reported only six times.

Contraindications to Immunization

Though complications following pertussis immunization may be serious and even fatal, they are extremely rare, and it is generally conceded that such immunization is undoubtedly worth while. It is well known that whooping-cough itself may produce serious complications, neurological and others, and the opinion of Brody and Sorley (1947) that "the risks of not immunizing against whooping-cough are vastly greater than the risks of immunizing" probably reflects the general view. Byers and Moll (1948) found that, in the same 10-year period during which their 15 cases of pertussis vaccine encephalopathy were admitted to the Boston Children's Hospital, 26 children suffering from the effects of encephalopathy complicating pertussis itself were admitted to the same hospital. Of these 26 children seven died during their acute illness, six had mental retardation, three had chronic convulsions, and one had cerebral palsy.

Opinions differ, however, on what constitute the contraindications to immunization. Some have regarded a personal or family history of convulsions or other neurological disorders as a definite contraindication (for instance, Cockburn, 1951; Tudor, 1951; Escardo and Vazquez, 1950; Köng, 1953; Sutherland, 1953). Others, while tending towards this viewpoint, have been less emphatic. Both Toomey (1949) and Grace (1950), for example, suggest a decreased dosage in these circumstances. As analysis of the reviewed data does not indicate any tendency for reactions to be associated particularly with larger doses, decreased dosage would not seem helpful, besides creating the problem of possible inadequate immunity. On the other hand, Melin (1953), basing his views on experience with epileptic children in Stockholm, actually recommends pertussis vaccination for children with convulsive disorders because he considers that "the risk of a seizured child contracting pertussis and eventually developing complications is more pronounced than the risk involved in the immunization procedure itself." Peterman (1953), Livingston (1953), and Byers (1953) have agreed with Melin.

The small number of reported suspect nervous systems, based on personal and family histories, in the cases reviewed would seem to bear out Livingston's (1953) doubt about children with convulsive disorders or tendencies being more likely to develop cerebral complications from pertussis immunizations than other children. The whole question depends on whether a child, in any given circumstances, both personal and environmental, is more likely to contract pertussis with serious complications therefrom than he is to develop serious sequelae from pertussis inoculation, and this is a matter not easily settled. On one point, however, there appears to be no room for controversy, and this is that *any* suggestion of a neurological reaction to a pertussis inoculation should be an *absolute* contraindication to further inoculation. This is forcefully illustrated by the fact that of the seven patients who had neurological sequelae after more than one injection two died and four were left with grave complications.

Allergy is sometimes considered a contraindication to inoculation. Köng (1953) lists allergic diseases among his contraindications, and Miller (1951) considers fractional doses advisable in asthmatic children. Halpern and Halpern (1955) feel that it may be advisable to administer smaller doses more frequently in older, highly allergic children. The few cases among those reviewed where a personal or family history of allergy was reported suggest that it is perhaps over-cautious to consider this as a contraindication.

Some authors, amongst them Miller (1951), Cockburn (1953), and Sutherland (1953), have recommended that inoculations should not be undertaken while a child is unfit or suffering from acute illness of any sort. While there appears to be no direct evidence that reactions are more likely under such circumstances, it seems a reasonable

precaution to avoid provoking a possible reaction at a time when resistance is likely to be relatively low.

Summary

A case is reported of an 8-months-old normal child who, within 24 hours of a combined diphtheria–pertussis inoculation, became pyrexial, drowsy, and hypotonic. Convulsions and evidence of mental deterioration followed rapidly. At 3 years of age convulsions still persisted and mental retardation was gross (I.Q.=23).

Review is made of 107 cases of neurological complications of pertussis inoculation reported in the literature. Males predominated; reactions occurred in all age groups in which immunizations were done, irrespective of the dosage used, and followed first or subsequent inoculations. A wide variety of vaccines, single and combined, were implicated. Past personal and family histories indicated relatively few instances of neurological or allergic abnormalities. The early onset of neurological symptoms was characteristic, with changes of consciousness and convulsions as the most striking features. Pareses or paralyses were not infrequent, and eight children died within 48 hours of inoculation. Follow-up revealed a recovery rate of about 50%, a persisting morbidity rate (physical and/or mental) of about 30%, and a mortality rate of about 15%.

The question of aetiology is considered and contra-indications are discussed. The value of pertussis immunization is emphasized, as is the grave danger of further inoculations when a previous one has produced any suggestion of a neurological reaction.

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THE NEUROLOGICAL COMPLICATIONS OF MUMPS

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The neurological complications of mumps have been recognized since the eighteenth century, and a number of reports have appeared in the European and American literature describing various forms and the frequency with which they occur. Thus in 1911 Doptor reviewed 1,700 cases of mumps and estimated that 9.8% showed meningeal symptoms. Laurence and McGavin (1948) found 60 cases in an epidemic involving 208 New Zealand Service men; and Frankland (1941), in discussing an outbreak of 234 cases, put the incidence of meningitis as high as 30%. On the other hand, Paddock (1932) and Coe (1945) found neurological involvement in only 0.15–0.5% of their series, which were less selective and covered a wider age range.

It has been suggested that differences in frequency of meningitis in various epidemics are due to variations in resistance to infection, perhaps due to racial factors or to an altered virulence of the mumps virus leading to an increased affinity for nervous tissue. It is partly accounted for by the different criteria which have been used in the diagnosis of meningitis, some authors relying on symptoms, others on symptoms and physical signs, and some on the alterations in cerebrospinal fluid. To add to the confusion, it has been repeatedly confirmed, since Lavergne's observation in 1938, that cerebrospinal pleocytosis may occur in uncomplicated cases of mumps (Finkelstein, 1938) or even in contacts showing no signs of mumps (Frankland, 1941), and that meningeal symptoms may precede parotitis by as much as ten days (Bedingfield, 1927; Frankland, 1941).

These facts led Doptor and others to the view that the mumps virus is primarily neurotropic and that involvement of the parotid glands occurs as a secondary and not invariable complication. The existence of a separate neurotropic strain of the virus has not received much support (Macrae and Campbell, 1949), and Gordon (1927) was able to produce a fatal meningo-encephalitis in a monkey by intracerebral inoculation of material from throat-washings of uncomplicated cases. No correlation has been found between the occurrence of nervous complications and the severity of parotid disease or of epididymo-orchitis (Holden, Eagles, and Stevens, 1946).

Mumps meningitis is a remarkably benign condition usually appearing within a few days of the parotid enlargement and recovering without complications in three to four days; occasionally it may precede parotitis or occur alone. The cerebrospinal fluid contains a variable number of lymphocytes (10–1,000 per c.mm.) with slight increase in protein and normal values for chloride and glucose. Mumps virus has been isolated from the spinal fluid (Henle and McDougall, 1947).

The major neurological complications are much less common (approximately 1 in 6,000) and have been

reviewed by Miller, Stanton, and Gibbons (1956). They may occur at the time of parotitis or up to 23 days afterwards, the average latent period being 7.2 days. Encephalitis cases are less rare than the other varieties —myelitis, polyradiculitis, and polyneuritis. Mental symptoms are prominent in encephalitis, and clinical features include drowsiness, convulsions, headache, psychoses, ataxia, and hemiplegia. Neck stiffness, involuntary movements, increased reflexes, and extensor plantar responses may be found. Deep coma may occur, and is an unfavourable prognostic sign. The cerebrospinal fluid often shows a lymphocytosis, but may be normal. Death occurs in approximately 20% of cases, and 33% of those who recover may show major sequelae consisting of hemiplegia, ataxia, and involuntary movements.

Fatal cases show a patchy perivenular demyelination similar to that seen following other post-infective encephalitides (Donohue, Playfair, and Whitaker, 1955).

Cranial nerve palsies involving the optic, facial, trigeminal, or oculomotor nerves may occur (Laurence and McGavin, 1948; Macrae and Campbell, 1949), and the important complication of labyrinthitis may be permanent and unassociated with signs of neurological damage. Local weakness of the limbs with transient loss of tendon reflexes and subjective sensory disturbance has been described (Lightwood, 1946; Laurence and McGavin, 1948).

In the following report 18 cases of meningitis and one of encephalitis occurring in the course of a mumps epidemic are described.

Incidence

During February–October, 1956, there was an epidemic of mumps in Gurkha troops stationed at Sungei Patani, Malaya. A total of 287 cases occurred, and 84% of the patients came from "Recruit Company" and "Boys' Company," aged 14–17. A number of those infected had arrived from widely scattered areas in Nepal two months previously.

The infection reached a peak in June, when there were 58 cases.

In the great majority the disease ran a benign course over a few days, but in the latter part of the epidemic meningitis began to appear, reaching a maximum in July, when there were 12 cases, one in every five being affected.

Thirteen cases had salivary glandular enlargement and meningitis; one had parotitis, orchitis, and meningitis; one had orchitis and meningitis; and three had meningitis alone.

TABLE I.—*Onset of Meningitis Related to Appearance of Parotitis*

	Days Before		Appearance of Parotitis	Days After								
	2	1	0	1	2	3	4	5	6	7	8	9	10
Cases of meningitis ..	1			1	1	2	4	1	1		2		1

The occurrence of these events is shown in Table I; it will be seen that in one case the meningitis preceded the parotitis by two days.

In the three cases presenting with meningitis alone there was no opportunity of confirming the diagnosis by serological means as described by Kilham, Levens, and Enders (1949), but, in view of their similar benign course and the presence of an epidemic, it was assumed that they were variants of the same malady.

The incidence of all complications is set out in Table II, and it will be noted that, in contrast to meningitis, orchitis occurred in sporadic fashion evenly distributed throughout the epidemic.

TABLE II.—*Incidence of Complications*

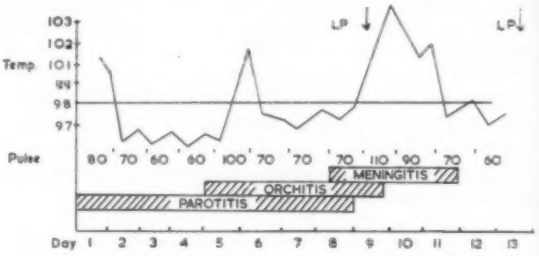
	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Total
Cases admitted	13	39	29	41	58	51	35	21	287
Uncomplicated	11	33	24	31	50	32	23	15	219
Orchitis ..	2	6	5	10	6	9	7	3	48
Meningitis ..					2	12	3	1	18
Encephalitis							1		1
Percentage incidence of meningitis					3·4	23·5	8·6	5·0	6·3

Clinical Features

Meningitis (18 cases)

The patients reached hospital on the first or second day following the appearance of parotitis. They were usually pyrexial, but in good general condition and reluctant to be confined to bed.

The pyrexia settled in 48 hours, but with the onset of meningitis it recurred (see Chart), and the cheerful swollen



Case 14. Boy aged 15. Temperature and pulse rate during illness.

faces were transformed overnight by expressions of extreme misery. The patients lay curled up in bed, complaining of severe headache and photophobia and refusing food and drink with such persistence that some had to be given fluids by tube. Vomiting occurred frequently and some had pain in the muscles of the legs.

On examination the most prominent finding was rigidity of the spine, which moved "in one piece" if an attempt was made to flex the neck. Kernig's sign was positive and there was slight muscle tenderness in the calves but no other objective neurological signs. Nystagmus, which had been reported in this condition, was not seen, and tendon reflexes were unaltered.

All the patients were irritable when disturbed and resented examination, but when induced to talk they seemed rational. They tended to spend a large part of the day asleep, but there was no nocturnal restlessness. The headache responded to aspirin in large doses, and appeared to be somewhat relieved by lumbar puncture.

The urine often contained ketone bodies but no albumin, and white-cell estimations showed values of 8,000–12,000 per c.mm., with a normal differential count. Recovery was rapid and complete in two to three days, and neurological examination four months later was negative. Two boys were thought by their instructors to be slower mentally after the illness, but apart from this equivocal finding there were no sequelae.

Cerebrospinal fluid was examined in all cases, and was usually repeated after 10 days. The results are summarized in Table III.

The cellular reaction was predominantly lymphocytic, although up to 60% of polymorphs was not unusual in the early stages. Estimations done later in the disease invariably

TABLE III

Case No.	Day of Disease	Fluid	Cells /c.mm.	Lymphocytes %	Polymorphs %	Protein mg./100 ml.	Chlorides mg./100 ml.	Sugar mg./100 ml.	Remarks
1	3	Turbid	230	60	40	48	750	57	Parotitis, meningitis
	9	,,	340	90	10	55	730	56	
	20	Clear	760	70	30	37			
2	5	,,	4	50	50	97	720	50	,,
	8	Turbid	140	35	65	95	690	52	
3	6	,,	940	50	50	240	690	55	,,
	16	Clear	2			37	760		
4	5	,,	6			49		55	,,
	12	,,	10	30	70	64	730		
5	3	Turbid	780	95	5	60	760		,,
6	7	,,	430	84	16	62	715	54	,,
		,,	60	80	20	47	740	45	
7	11	,,	930	80	20	95	670	69	,,
	17	Clear	Nil			49			
8	2	Turbid	460	32	68	94	760	45	Meningitis preceded parotitis
9	4	,,	130	38	62	25	730	41	Parotitis, meningitis
	16	Clear	1			17			
10	3	Turbid	1,260	70	30	110	740	68	,,
	14	Clear	3			47	670	46	
11	6	Turbid	86	70	30	80	720	82	,,
	14	Clear	9	88	12	58	740	64	
12	6	Turbid	340	90	10	60	750	36	,,
	13	Clear	80				710	58	
13	9	Turbid	370	90	10	70	730	65	,,
	20	Clear	30	90	10	25			
14	9	Turbid	480	90	10	61	710	34	Parotitis, meningitis, orchitis
	14	Clear	7	56	44	30	700	49	
15	5	Turbid	720	98	2	72	660	39	Orchitis, meningitis
16	3	Clear	80	28	72	100	720	50	Meningitis alone
17	4	Turbid	250	96	4	90	700	48	,,
		Clear	6			50			
18	2	Turbid	400	60	40	75	750		,,
	7	Clear	29	75	25	210	730	45	
19	11	,,	1			20			Parotitis, encephalitis

showed a preponderance of lymphocytes. Total counts in the acute stage varied between 200 and 800 cells per c.mm., falling rapidly in a few days, but in some cases being still significantly raised at the end of two weeks, when patients were asymptomatic and seemed fit for discharge. The protein was raised in proportion, with a usual reading at 60–100 mg. per 100 ml., and chloride and sugar estimations showed no significant abnormality. Six uncomplicated cases of mumps from the same epidemic and at the same time were subjected to lumbar puncture. Results were normal in every respect.

Encephalitis (1 case)

A previously healthy boy aged 14 with no past or family history of psychiatric disturbance was admitted with swelling of parotid and submandibular glands present for two days. He was slightly pyrexial on admission—temperature 99.4° F. (37.4° C.).

The swelling subsided over the first week, but on the ninth day he began to vomit and refused all nourishment. Over the course of 24 hours he became speechless and extremely drowsy, with episodes of mania when disturbed. In these he struggled violently with the attendants, grinding his teeth and biting anyone within reach, although never speaking a word. Headache was not prominent, but he appeared to have some abdominal pain. Temperature and pulse were normal. He was restless at night and slept fitfully during the day. He developed retention of urine, requiring catheterization.

Satisfactory examination of the nervous system was well-nigh impossible, but there was no gross disturbance of cranial nerves or limbs; there were no signs of meningeal irritation. The tendon reflexes were present and equal and the plantar responses were flexor. Lumbar puncture yielded normal cerebrospinal fluid under increased pressure. The urine contained no albumin or sugar and the urinary diastase was normal. Blood-sugar and blood-urea estimations gave no additional information.

After three days of mutism and grossly abnormal behaviour he began to improve; speech returned after a further 24 hours, and within a week he was completely recovered, having an amnesia extending over the encephalitis episode. Examination at this time and again three months later revealed no neurological or psychiatric abnormality and his subsequent mental state is reported as unchanged.

Comment.—There are many resemblances to previously reported cases, notably the acute onset nine days after the appearance of parotitis, and the predominance of mental over physical features. The absence of meningeal symptoms and of cerebrospinal fluid changes is well recognized. Unusual features are retention of urine unaccompanied by any signs of spinal-cord involvement, and the occurrence of mutism.

Discussion

The cases reported above conform to the description given by previous authors. They emphasize the important clinical distinction to be made between meningitis, a common and relatively trivial complication, and encephalitis, a serious condition with high mortality. The reason why the nervous system reacts in these two ways to infection with the mumps virus is not fully understood, although it has been the subject of much recent research.

The clinical syndrome of meningeal irritation, combined with the finding of cerebrospinal pleocytosis and the fact that the virus can be isolated from the spinal fluid, makes it likely that the changes of mumps meningitis are due to the direct action of the virus. In the present epidemic, an unusual one in that it occurred in an adolescent community only recently exposed to mumps, the overall incidence of meningitis (6.3%) is not unduly high, but it is significant that all the meningitic cases occurred in the course of a few weeks in the latter part of the epidemic. This suggests that the virus acquired an unusual degree of neurotropism during the epidemic, reaching a peak in July, when the incidence of meningitis was 23%. There was no increase in the frequency of orchitis or other visceral complication at this time.

If separate strains of virus with increased affinity for nervous tissue do arise in this way the incidence of meningitis in an epidemic of mumps is related more to the properties of the virus than to the state of immunity of the patients. This may help to explain the widely differing estimates of the frequency of meningitis as reported by various authors. It is, of course, also possible that the meningitic cases were due to a superadded infection with an unrelated virus, but this seems unlikely, and has received no support from serological studies (Kilham, Levens, and Enders, 1949).

The occurrence in the present series of two cases of meningitis without other features of mumps serves as a reminder that mumps should be included in the differential diagnosis of benign lymphocytic meningitis. The identity of the infection may be obvious during an epidemic, but isolated cases may give rise to difficulty, which is only solved by routine serological testing. In a recent series (Adair, Gauld, and Smadel, 1953) mumps was found to account for 12% of 854 cases of aseptic meningitis in America, and serological studies have been confirmed by the isolation of the virus from the spinal fluid (Kilham, Levens, and Enders, 1949).

Although most authorities agree in attributing meningitis to the direct action of the virus, there are conflicting views on the aetiology of encephalitis. This has been attributed to a further extension of the virus from the subarachnoid space into the neuraxis, possibly as a result of a high degree of neurotropism or a low resistance on the part of the patient

(Donohue, Playfair, and Whitaker, 1955). However, the latent period before the appearance of encephalitis and the occasional absence of meningeal symptoms and of cerebrospinal pleocytosis (as shown by the case reported here) do not support this view, and favour a primarily encephalitic process rather than a spread from the meninges.

The clinical resemblance between mumps encephalitis and the encephalitis which may follow measles, varicella, and rubella, and the fact that the histological appearances of perivascular demyelination are common to them all, suggest that they arise from the same pathological process (Miller, Stanton, and Gibbons, 1956). The nature of this process is unknown, but it may be a non-specific allergic reaction to virus protein (Miller and Evans, 1953), and similar lesions have been produced experimentally by the injection of brain material with adjuvants (Lumsden, 1949).

Summary

Previous reports on the neurological complications of mumps are reviewed. Lymphocytic meningitis is not uncommon, and recovery is full in a few days. Encephalitis is extremely rare, and has a mortality of 20%.

Eighteen cases of meningitis and one of encephalitis arising in an epidemic of 287 cases are described. The meningitic cases occurred only during the latter part of the epidemic.

The aetiology of the neurological sequelae is briefly discussed. Meningitis may well be due to the emergence of strains of viruses of increased neurotropism during an epidemic.

We wish to thank the Director of Medical Services, R.A.M.C., for permission to publish.

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Medical Memorandum

Advantages of "Polythene" Ring Pessaries

The advances achieved in surgical technique and, more particularly, in the art of anaesthesia in the past twenty years have made the surgical repair of genital prolapse the ideal method of treating this common disability. However, in spite of these advances there are some women whom it would be too great a risk to subject to an operative cure. We find this group to constitute less than 3% of the total number of patients with symptoms caused by a genital prolapse. A second group of patients complaining of genital prolapse, on whom a surgical repair is not immediately desirable, are the women of child-bearing years who have either been recently delivered or are about to embark on another pregnancy. A third group of patients refuse to undergo a surgical repair. These three groups can have their symptoms relieved by the fitting of a ring pessary into the vagina.

The ideal ring pessary should possess the following properties. (1) It should be made of a substance that is inert and produces no tissue reaction that will lead to a malignant change in the vaginal walls and no offensive vaginal discharge. (2) It should be sufficiently compressible to introduce through a small vaginal introitus, yet possess enough elasticity to regain its shape when introduced into the vagina, and it should not alter in shape or in its physical properties with prolonged use. (3) It should be technically easy to manufacture and cheap to produce.

The many varieties of material from which ring pessaries have been constructed can be divided into those of the preplastic era and those of the plastic era. The former group are the rubber watchspring pessary and the vulcanite pessary. The watchspring pessary is compressible, but it produces an offensive vaginal discharge. The vulcanite pessary has both the disadvantage of incompressibility and the property of producing leucorrhoea. Pessaries made from the many varieties of plastics can be constructed of compressible material or a plastic that is for practical purposes incompressible.

The flexibility of plastics such as P.V.C. depends on the presence of a plasticizer. The majority of plasticizers are toxic to tissues when in contact with them for any length of time and may induce a malignant tissue response. A plasticizer with a low vapour pressure, such as dioctylphthalate, does not produce a tissue reaction. It has, however, the disadvantage of escaping from the material with which it has been mixed, and brittleness and loss of flexibility follow.

Pure polythene, however, is chemically almost inert and has been buried in living human tissues for long periods of time without producing any toxic reaction. It is, furthermore, sufficiently flexible and compressible to use as a pessary and firm enough to support the vaginal walls and uterus in a genital prolapse. The material does not lose its flexibility whilst in the vagina. We have had experience of using the pessaries for three years in the vagina without any apparent physical change occurring in the material. The management of the cases treated with polythene pessaries does not vary from pessaries of other materials.

Patients are examined every three months, the vaginal walls are inspected for evidence of ulceration, and the pessary is washed and replaced.

Polythene is made in a number of different grades which, chemically speaking, differ only in their molecular weight. There is very little variation in the physical properties between different grades except at temperatures up to 100° or below 0° C. In particular the modulus of elasticity which determines the flexibility of the product is much the same for all grades at normal temperatures. The only advantage of using a grade of higher molecular weight is that it can be boiled without danger of deformation. From the manufacturer's point of view, however, the light molecular weights are easier to mould. For these reasons the choice of grade is not very important. A ¼ in. (0.6 cm.) diameter cross-section provides the necessary flexibility and at the same time is thick enough to support the vaginal walls yet will not cause ulceration.

Cost.—The polythene pessary is cheaper to manufacture than the rubber-ring pessary and its life is infinitely longer; while a rubber ring has a life of only six months at the most, a polythene pessary retains its shape, smooth surface, and flexibility for years.

We are indebted to Mr. D. Annat, M.P.S., chief pharmacist, Stoke Mandeville Hospital, for negotiating the original samples of plastic and polythene and organizing the supplies of the polythene pessaries from the manufacturers, Portland Plastics Ltd., Hythe, Kent.

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Reviews

LAW AND ETHICS FOR DOCTORS

Law and Ethics for Doctors. With a Section on General Practice in the National Health Service. By Stephen J. Hadfield, M.A., M.B., B.Chir.(Cantab.). With contributed sections on Negligence, by W. G. Hawkins and the late W. Mair; Superannuation, by L. S. Potter, M.B., Ch.B.; and Income Tax, by W. Donald, C.A. (Pp. 399+xvi. 42s.) London: Eyre and Spottiswoode. 1958.

This excellent book treats with accuracy and judgment the many practical problems which may nowadays confront a doctor outside the purely clinical field. Some of these problems are happily rare in their incidence, but a doctor's career may nevertheless be a good deal influenced by the way in which he handles, for example, a complaint by a colleague of unethical conduct on his part, an allegation of negligence, or an appearance in a court of law. Other difficulties, such as those raised by cases of mental disorder, by questions of certification, or by dangerous drugs and poisons, may be less acute in themselves but are apt to recur more frequently. In his book, which rests on a comprehensive plan, Dr. Hadfield sets out the legal, ethical, and practical considerations which should guide a doctor when he encounters these and many other problems. While offering balanced and realistic advice, in which he has been able to draw on his experience as an Assistant Secretary of the British Medical Association, Dr. Hadfield does not omit to stress the need for seeking early advice in some cases—for example, from a defence organization—before any "home-composed reply" is posted or other irremediable action is taken.

Much of the latter part of the book deals more particularly with general practice in the National Health Service. Apart from supplementary information given in appendices, the aim has been to summarize and throw light upon the lengthy regulations, as distinct from reproducing their terms in full.

A foreword to the book has been contributed by Dr. Solomon Wand.

WALTER PYKE-LEES.

SURGERY AND THE LABORATORY

An Introduction to Experimental Surgical Studies. By W. J. Dempster, F.R.C.S. (Pp. 463; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1957.

The experimental laboratory has made notable contributions to the progress of modern surgery—sometimes in respect of technical problems that are purely surgical, but often in respect of fundamental physiological, biophysical, and biochemical problems that are equally the concern of all the disciplines of medicine in its widest sense. In fact, it is the almost automatic reference of clinical difficulties to the laboratory—the complete if tardy permeation of medicine by the experimental outlook and method of Harvey and Hunter and Lister—that has transformed medicine from an art to a science. Unfortunately the fruits of much research are scattered widely in a now voluminous literature; the tyro has difficulty in finding out what has or has not been submitted to critical experimental scrutiny; and the ageing clinician has certainly not the time, even if he has the inclination, to plough through so many original papers. An introduction—or a guide—to what has been accomplished or is at present under investigation is therefore a welcome and important addition to medical literature. Nevertheless—and possibly because one had hoped for more—the present book is a little disappointing. The author is widely recognized as a distinguished and versatile and original research worker, and in those sections of his text that deal with his own interests—the regeneration of tissues, wound healing, and transplantation and tissue and organ grafting—his account is, on the whole, judicious and critical and comprehensive, though he makes some surprising and incorrect pronouncements—for example, that surgeons have abandoned arterial grafts. He is on less sure ground in his review and criticism of research in such special fields as the gastro-intestinal tract and the liver; here there are some surprising omissions, some obviously personal—and unsupported—opinions, and a bibliography that is less comprehensive than elsewhere. This may be due to a desire to keep the book within reasonable compass; equally it may reflect the impossibility, as on the clinical side, of a single individual's being able to master all facets of surgery.

These friendly criticisms do not detract from the value of a book which I have vastly enjoyed, and greatly admired for its erudition. Indeed, it could form the basis for a longer and more comprehensive book—possibly collaborative—that would enhance the reputation of both the author and his school. If this should happen, or when a second edition of the present work is called for, perhaps Mr. Dempster would delete the somewhat pontifical injunction on page 203 to the effect that "the reader is well advised to take cognizance of the contributions being made to medicine by the basic sciences." There are disadvantages in long residence in any "ivory tower."

JOHN BRUCE.

FAMILY LIFE OF THE AGED

The Family Life of Old People: An Inquiry in East London. By Peter Townsend. Foreword by J. H. Sheldon. (Pp. 284+xvi. 30s.) London: Routledge and Kegan Paul. 1957.

Mr. Townsend has carried out an interesting and important inquiry into the lives of a random sample of 200 old people living in the borough of Bethnal Green. This survey, and the conclusions to be drawn from it, make an important contribution to our knowledge of how the old, and in particular the needy old, live. Mr. Townsend is careful to point out that his inquiries were confined to one only of the metropolitan boroughs, and that his conclusions cannot therefore be universally applied. But there is little, if anything, in his conclusions which differs from those arrived at in comparable, if not precisely similar, surveys that have been carried out in other parts of the country.

Although a large number of the old persons interviewed lived alone, it was interesting to read how few were really isolated: most had relatives living in the borough who were in regular touch with them, and it is heartening to read of the important part still played by the grandmothers in what may be called the "three tier" family. They help to prepare meals, to take care of the grandchildren, and in many other ways continue to play their full part in the life of the family. Retirement of men, particularly if it is enforced on healthy persons of 65, is a real tragedy. The fall in income and in status leads to a loss of friends and diminution of social activities. Jobs for the retired are not easy to find, and are only too often of a character which is uninteresting and humiliating. Yet occupation can be of considerable value in maintaining health, both mental and physical. It is interesting to note the increased proportion of the unmarried or childless who enter the wards of the local geriatric hospital; this further emphasizes the ill effects that loneliness and friendlessness have upon the aged. Boredom, due to lack of suitable occupation, is one of the terrors of old age: one has only to examine any of the well-organized schemes for the employment of the elderly to realize their value. Mr. Townsend's book will provide much valuable information for those who have the welfare and the well-being of the aged at heart.

AMULREE.

THE HINDU PERSONALITY

The Twice-Born: A Study of a Community of High-caste Hindus. By G. Morris Carstairs. Preface by Margaret Mead. (Pp. 343. 30s.) London: The Hogarth Press. 1957.

This is a strangely old-fashioned book for a young author to write. It is perhaps the last of attempts begun in the 1930's to apply psychological theories and psycho-analytical

methods elaborated in the cultures of the West to people and to groups in alien societies. Apart from the epistemological objections, such works (associated notably with the name of Margaret Mead, who provides a brief preface to the present book) have been criticized for their lack of the prerequisite analysis of the social forms within which personalities emerge, loose handling of the evidence, and an over-reliance upon the popularity of the topic. Dr. Carstairs, more sober and modest in style, does not entirely avoid the failings of his predecessors.

The material offered is drawn from a village in Rajputana where the author compiled 45 case histories derived from four castes. The argument attempts to show that there are recognizable personality types corresponding to each of the first three castes (the fourth is marginal), that there is a more basic personality type common to all three, and that finally this basic personality is not without relevance to an understanding of the Hindu personality as such. Dr. Carstairs by no means makes it clear at which level of abstraction his generalizations are to apply. I am surprised to find him ready to comment, from his village data, upon the behaviour of politicians in Delhi.

The most satisfactory sections of the book are the case histories of three informants together with the Rorschach tests analysed by Dr. Rosemary Gordon. There are only three objections to be made here. First, on methodological grounds one may wonder whether Dr. Carstairs is correct in taking as his examples his English-speaking informants. It seems probable that "the distorting influence of translation" which he seeks to avoid is a lesser hindrance to understanding than the imperfect English of villagers. Secondly, the paranoid and suppressed homosexual tendencies which are stressed as elements in the basic Hindu personality do not emerge in the first two examples, and there is only a possible element of homosexuality in the emotional friendship of the third, who is not in fact a member of the local community studied. Thirdly, a query by Dr. Gordon raises serious epistemological doubts. She suggests (p. 325) that differences in cultural life, religious symbolism, and so on make it difficult for a European analyst to score confidently upon the Hindu responses to Rorschach tests. One cannot prevent this doubt extending itself to the range of technical vocabulary derived from psychopathology in the West. Terms like "paranoia" have significance and value only in relation to their opposites—that is, to states of mind regarded as normal in a given society. If paranoia characterizes a whole society and is consequently normal in that society, we have either to redefine our terms completely or else be a good deal more circumspect in our dealings with any of our friends who happen to be Hindus.

The over-all criticism rests finally not upon the relation of evidence offered to conclusion drawn, unsatisfactory as it is. More fundamental are doubts concerning the *kind* of knowledge sought and the logical premises of the attempt.

D. F. POCOCK.

ALDOSTERONE

An International Symposium on Aldosterone. Edited by Alex F. Muller, M.D., and Cecilia M. O'Connor, B.Sc. (Pp. 232+x; illustrated. 40s.) London: J. and A. Churchill, Ltd. 1958.

This book is a detailed report of contributions by recognized authorities to specialized fields of research on aldosterone. It is based on 13 papers of high standard, followed by detailed discussions, which as usual contain a mass of useful information. The organizers of the symposium, held in Geneva last year—Professor R. Mach and his Swiss colleagues—are to be congratulated, and the editors too have done their work well. I feel that the technical production of the book itself does not give the ease of reading characteristic of earlier volumes by the same publisher; in particular, some of the diagrams are a little obscure and some are accompanied by liberal amounts of excessively small print.

It would be invidious to draw distinction between the various contributions, but chapters that might be expected to have the most general appeal include those on the site of aldosterone secretion by Giroud and colleagues, its metabolism by Tait and colleagues, and oedema by Wolff and colleagues. Those by Garrod and colleagues and Stanbury and colleagues contain useful review material on so-called primary aldosteronism and renal abnormalities in relation to aldosterone respectively.

F. T. G. PRUNTY.

MEDICINE FOR DENTISTS

Oral Medicine: Diagnosis and Treatment. By Lester W. Burket, A.B., D.D.S., M.D., Sc.D. With a Chapter on Oral Cancer by S. Gordon Castigliano, B.A., B.S., M.D., F.A.C.S. Third edition. (Pp. 558+xxi; illustrated. £5.) London: Pitman Medical Publishing Co., Ltd. 1957.

This is a further edition of an already well-known book. Many chapters have been rewritten and therapy has been brought up to date. A special colour atlas of common oral lesions is now included with a chapter on oral cancer. The attempt to bridge the gap between general medical conditions with specific signs and symptoms in the oral cavity, and purely local conditions, is difficult to achieve. It might perhaps at times have been better to have left these conditions as something of which the dental surgeon should have some knowledge, rather than try to link them, often on very tenuous grounds, with some oral manifestations—for example, urogenital conditions, appendicitis, etc. On the whole, however, this is a very useful book, but I hesitate to think what would happen in this country if the overworked dental hospitals and practitioners were asked to use the questionary as given to all patients at the University of Pennsylvania School of Dentistry, where 80 questions have to be answered by the patient before treatment is started, including ones such as No. 78, "Do you wish that you always had someone at your side to advise you?" and No. 80, "Do you feel you mix well with people?" The instructions are "to answer all questions and if you are not sure—guess."

A. B. MACGREGOR.

REGIONAL BLOCK

Regional Block: A Handbook for Use in the Clinical Practice of Medicine and Surgery. By Daniel C. Moore, M.D. Second edition. (Pp. 393+xvi; illustrated. 80s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

The first edition of this excellent manual achieved the success which was predicted for it. The second edition will be as eagerly sought after as its predecessor. On every page it bears the hallmark of long personal experience by the author. The illustrations and text, as before, are particularly clear, and enable anyone who takes sufficient care to attain success with these methods of local analgesia. The production is once again of a high standard, paper, printing, and binding being excellent.

W. W. MUSHIN.

A small handbook on *Respiratory Disease and the General Practitioner*, by C. H. C. Toussaint, has been published by the National Association for the Prevention of Tuberculosis (28 pages, illustrated; 7s. 6d.). It contains practical advice on the diagnosis of respiratory tuberculosis and bronchial carcinoma and on the management of bronchitis. Special emphasis is laid on the value of diagnostic radiography.

Modern Drug Treatment in Tuberculosis, by J. D. Ross (National Association for the Prevention of Tuberculosis, 47 pages; 5s.), is intended primarily for nurses. It describes the use of streptomycin, P.A.S., isoniazid, viomycin, pyrazinamide, oxytetracycline, cycloserine, and thiosemicarbazones. A chapter on drug resistance is included.

The National Library of Medicine Catalog for 1957 provides an author and subject catalogue of the additions to that library during the period January–October, 1957. Besides new works the catalogue records titles of older material recatalogued during the period. It is obtainable from the Card Division, Library of Congress, Washington, 25, D.C., U.S.A., price $17.50.

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TEN YEARS

Ten years ago, as both of the plebiscites of 1948 showed, a majority of the profession was opposed to entering the National Health Service. A plebiscite to-day, exactly ten years later, would undoubtedly show a majority to be highly critical of the Service and in favour of reform. Our correspondence columns have shown that the desire for reform is widespread. At Birmingham next week the Representative Body will hear from the Chairman of Council, Dr. S. Wand, that the Royal Colleges in England, to be joined soon, it is hoped, by the Royal Scottish Corporations, the Society of Medical Officers of Health, and the College of General Practitioners, will co-operate with the B.M.A. in a review of the health services of Great Britain. A committee widely representative of the whole profession will thus set out to discover just what general practitioners, consultants and specialists, professors and teachers, and medical officers of health think of the N.H.S. The intention behind this exercise is to bring together the facts, to sort them out and to classify them, to make comparisons with similar facts in other countries, and to make recommendations which may lead to a service in which doctors can work more happily and efficiently than they do at present. The end of the first decade of a social revolution finds the profession in no mood for jubilation. The politicians must inwardly regret their enormous errors of calculation. Whatever benefits it has received the public is beginning uneasily to wonder whether the price has not been too high in this free-for-all scramble for medical attention. It is at least good that the doctors of this country are entering the second decade with a determination to put aside their internal differences in order to find out just what the past ten years of experiment have added up to, and to decide what direction the medical profession shall take in the coming ten years.

In the *Supplement* this week is a symposium of articles written to mark the end of the first decade of the N.H.S. In it we have also brought together the principal resolutions on various aspects of the N.H.S. passed by the Representative Body: here for ready reference is a summary of the official policy of the Association. The two principal protagonists in the medical arena ten and more years ago were Dr. H. Guy Dain as Chairman of the Council of the B.M.A. and Lord Moran as President of the Royal College of Physicians. We have invited them to put down some of their reflections on the past decade. What they say has behind it the weight and authority of two men who more than any other were, ten and fifteen years ago, intimately involved in the intricacies of medical politics—the one predominantly concerned with the Association and the interests of the general practitioner, and the other with the problems of the hospital and consultant world. What is of special interest is that both these experienced Elder Statesmen of the profession throw out more than a hint that some form of direct charge should be made at least for some services. This is not exclusively a political issue. Doctors are, of course, concerned to see the N.H.S. solvent, to make sure that money that should be available for hospital development, for instance, is not thrown away on household remedies everyone used to buy for himself but now gets out of the Health Service. The politician averts his gaze from this and pretends it is the expensive proprietaries that send the drug bill soaring. The doctor wants to ensure that there is no barrier between the patient and the life-saving or disease-preventing remedy. He also wants to ensure that the public uses the Service in a responsible way. He casts an envious glance at Australia, where, as Dr. Ronald R. Winton puts it in his article in the *Supplement*, "the view has prevailed that the benevolent but bureaucratic grandfather who presides over the Welfare State is not for us. Various social services provide for those with genuine needs, but a premium is still put on self-reliance and independence of spirit." This is well said, and many doctors in Britain would echo his words. Quite apart, therefore, from any question of financial solvency, many doctors now would like to see the patient taking a greater share of direct responsibility for his own physical welfare, and it is interesting to note the views of Dr. Dain and Lord Moran on this.

We should, Dr. Dain says, have a look at health services in other countries, and in this connexion he refers to the fee-per-service system: "Both doctors and patients would seem to set a better value on a service if some payment was made at the time." The articles in this week's *Supplement* show that our colleagues in Australia, Canada, and New Zealand are firmly opposed to the capitation method. What seems to be behind this opposition is a dislike of a uniform levelling of reward for work done which

takes little regard of the diversity of human ability. The great virtue of the merit awards for consultants was—and is—that they take this diversity into account. We have criticized certain aspects of this system in the past, but at the end of ten years it is true to say that consultants as a whole accept merit awards as a valuable stimulus to effort and a practical recognition of the results of that effort and ability. Lord Moran's name has been closely linked with this novel experiment, and at the end of a decade of operation he can with justifiable satisfaction record that he has converted the Treasury to his view as well as his fellow consultants. But he has his fears for the future of medicine. Does medicine offer a challenge to achievement to those seeking to enter its portals? Or is it just one more port of security for the safe but mediocre minds for whom the Welfare State has such a dreary appeal? There is reason to fear that medicine may be attracting less of the available top talent than it used to do: and if this can be laid at the door of the N.H.S. then the aims of the Spens Reports have not been fulfilled—which is not surprising, as their terms have not been carried out.

Most people would agree with Dr. Dain that from the point of view of the public the Health Service has been a success. Many barriers that existed before have been removed, especially for those of moderate means. There has been a more even distribution of consultants throughout the country and a general increase of hospital facilities. But many of the benefits laid at the door of the N.H.S. more properly could be credited to the advances of modern medicine. One of the most remarkable of these has been in the field of medicinal therapeutics: yet we already hear the State managers growling at the pharmaceutical industry, whose participation in this phenomenal progress has been indispensable. British medicine to-day is at a high peak of achievement. In research, in ingenious experiment, in speculative energy, we can hold a candle to any other country in the world. But those who are paramount in these fields came into medicine before 1948. Will British medicine stand so high ten years hence? Unless we can be sure that it will, or at least create the conditions that make for excellence, then the N.H.S. may a decade from now be a perfect machine manned by an army of uniformed conductors but without a driver.

Among the articles in this week's *Supplement* appears one by Professor Paul F. Gemmill, who is a professor of economics in the University of Pennsylvania. He conducted a survey of his own in this country in 1956. It would be fair to judge that his conclusions were favourable to the N.H.S., and he has certainly tried to bring some kind of measurement into the matter. Yet his figures are disquieting. Nearly 40% of the general practitioners in his survey found the "paper work" burdensome. Nearly 50% of the doctors questioned said their time was *often* taken up with "very minor ailments." Only 11% said that these complaints of "very minor ailments" led to the prevention or detection of something more serious. But what will surprise many is the reply to the question put to patients by Professor Gemmill about a comparison of the medical services under N.H.S. with those before 1948: only 37% said the N.H.S. was better than what went before; 50% said the medical service to-day was about the same as it used to be; and 13% said conditions were actually worse. It is to be hoped that the implications of this result will be understood by the Conservative M.P. whose stupid and ill-informed observation is reported at the end of Professor Gemmill's interesting paper.

In this week's special *Supplement* we have not attempted to review the Act and its deficiencies, the numerous reports issued since 1948 such as the Goodenough, the Guillebaud, the Bradbeer, and so on. We have chosen, instead, to bring together by selection or by invitation contributions from men who are first and foremost individuals with minds of their own, and in particular from the two opening contributors, whose views have a historical interest in that they were the first actors on the stage set by Sir William Beveridge (as he then was) in 1942. No one—not even Professor Gemmill's slightly absurd politician—would repeat in all its detail the experiment of 1948 if given the chance to do so. It is no good crying over the milk that was spilled then by the pailful. The urgent task is to look into the future, to repair, to reconstruct, to liberate the spirit of medicine from the inept embrace of the bureaucrat.

The most promising sign is the coming together of the Royal Colleges with the B.M.A. and others to examine the immediate past ten years in order to plan more wisely for the next ten. It will be no easy task—there are bound to be setbacks and disappointments. But the leaders of the profession to-day recognize there is far more at stake than the prerogatives of this or that organization or institution. If July 5, 1968, is to witness a more happy kind of celebration than is possible to-day it will be the result, as much as anything else, of the co-operative movement towards reform being undertaken by the committee now moving into action as a result of the initiative of the B.M.A. and of its Chairman of Council, Dr. S. Wand.

CANCER RESEARCH

Under the auspices of the Union Internationale contre le Cancer, the Seventh International Cancer Congress will be held in London from July 6 to 12, with Sir Stanford Cade as president. It is now thirty years since the last international cancer congress took place in London, sponsored by the British Empire Cancer Campaign. In the interval congresses have been held in Madrid (1933), Brussels (1936), Atlantic City (1939), St. Louis (1947), Paris (1950), and Sao Paulo (1954), under the aegis of the Union Internationale. The proceedings of this series of meetings naturally provide a useful record of the development of cancer research over a period sufficiently long to show its main trends; and much will be learned from comparison of the London meeting of 1928 with that about to take place. The earlier meeting had Sir John Bland-Sutton as president, and its membership embraced a host of famous names. Its official report (edited by the late Professor Archibald Leitch, then director of the Research Institute of the Cancer Hospital) contained many useful papers on aetiology, the causative role of viruses, occupational cancer, the relative values of surgery and radiation, chemotherapy with heavy metals, early diagnosis, the biological effects of radium and *x* rays, and cancer of the lung—with a contribution by Sir Robert Hutchison on the increased frequency of this disease, which was then beginning to be suspected and defined, though very far from attaining its present spectacular dimensions. The expansion of cancer research in the intervening years is to some extent exemplified by the numbers who will attend the forthcoming Congress: in place of two or three hundred there will be nearly 2,000 from 63 different countries, including some 500 from the United States and 50 from the Soviet Union.

What is the present situation of cancer research and what are the prospects for the future? The two major aspects, clinical and experimental, are reflected in the programme of the Seventh Congress. The beginnings of cancer research in the earlier part of the nineteenth century—coincident with the rise of the cell theory—were followed by a long period of description and classification. This period certainly laid the foundations of our modern knowledge, but it was followed, inevitably, by a phase in which doubts arose about how much further progress could be expected from study of the disease in man alone. In turn this led to wider application of the experimental method—in this country through the establishment in 1902 of the laboratories of the Imperial Cancer Research Fund under the auspices of the Royal College of Surgeons of England and of the Royal College of Physicians of London, and in 1909 of the Research Institute of the Cancer Hospital. The clinical and pathological approach on the one hand, and the experimental approach on the other, are of course complementary, and must remain so. In spite of the difficulty in extracting fresh knowledge from study of the human disease alone, advances are still being made along this path, notably in the fields of statistics, demography, geographical pathology, and endocrine control, which is the subject of three papers in this issue by R. D. Bulbrook, F. C. Greenwood, G. J. Hadfield, and E. F. Scowen. We must not forget that the first essential clues to cancer causation came from clinical and occupational medicine alone. Yet there is equally no doubt of the power and flexibility of the experimental method. Employing it, the great E. F. Bashford, first director of the Imperial Cancer Research Fund, was able, in the ten years prior to the first world war and with the aid of a small but brilliant staff, to elucidate the basic characteristics of the cancer cell. Starting with a demonstration of the almost universal zoological distribution of the disease in nature, he was soon able to define, in terms of tissue immunology, the capacity of the cancer cell to propagate itself in serial transplantation. His genius is shown in a statement which he left us, forecasting in prophetic fashion the needs and development of cancer research. He realized, as did others, that the next great step forward must depend on the artificial production of the disease under experimental conditions at will. This is not the place to recount the many failures of such attempts. Eventually success came to the Japanese Yamagiwa and Ichikawa in 1915, when they were able to induce undoubted cancer by long-continued application of coal-tar—already incriminated in the causation of many forms of cancer occurring as an industrial hazard—to the skin of rabbits. The new Japanese discovery provided the means of tracing and identifying the agent responsible, and from the work of the late Sir Ernest Kennaway and his school at the Cancer Hospital in the nineteen-twenties and thirties the cancer-producing agent in pitch and coal-tar was ultimately defined as the polycyclic aromatic hydrocarbon 3:4-benzpyrene. Since that time many other types of chemical substance have been discovered, equally capable of producing cancer, and ranging from azo-dyestuffs and aromatic amines to polymers, plastics, and metals. In the past ten years fundamental information of great importance has been derived from study of the so-called alkylating carcinogens—nitrogen mustards, epoxides, ethyleneimines, and dimesyl compounds—the reactive side-chains of which may conceivably exert their chief effects against the integrity of the

nucleic acid structure. In addition, the same cancer-producing property is to be found in many kinds of radiation—infra-red, ultra-violet, *x* and gamma rays, alpha and beta radiation, and protons and neutrons.

Early in the history of cancer research two main conclusions were quickly reached: first, that the cancer cell and the normal embryonic cell are in many ways remarkably similar; and, secondly, that malignant change involves a reversion to a more primitive state and less specialized function. Modern research not only supports these conclusions but has added to them. Far from the cancer cell having acquired any new property, it appears to have lost something present in normal cells which is required for controlling their growth, so liberating permanently the suppressed growth potential that they had all along possessed. In the past ten years interest has extended from carcinogenic agents in their own right towards the means by which so many agents, chemically and physically diverse, can bring about malignant change. As to the production of cancer by chemical carcinogens, it appears that these may combine with substances responsible for cellular heredity and growth control, thus leading to elimination of the forces which ordinarily restrain the change to malignancy. Although the evidence is not yet conclusive this supports the view already suggested that the cancer cell is biochemically deficient, either in its growth-regulatory systems or in the hereditary material responsible for their synthesis. Apart from this as it were chemical interpretation, research workers, particularly in the U.S.A., have made notable advances in the past few years in the field of tumour viruses—advances in many cases proceeding directly from the discoveries of Ludwik Gross, whose paper on the viral aetiology of mouse leukaemia is printed in the opening pages of this issue. Discussion of these viruses will certainly have a prominent place in the proceedings of the Congress.

Complete knowledge of the attributes of the cancer cell, when this is obtained, will perhaps suggest, on a rational basis, the means of control. Meantime the chemotherapy of cancer has been making good progress, and it has been gratifying to see how the results of experimentation in animal species—in many instances, although not, of course, in all—have proved capable of clinical application in man. But cancer chemotherapy is still in its merest infancy, and the few advances that have been made do not as yet affect the treatment of cancer as a whole. Almost certainly the present chemical remedies will be superseded by far more specific molecules, which will possibly restore the control of cell division and growth which the cancer cell appears to lack. When the suppression of the disease is achieved, the success will have been made possible by one thing alone—that international co-operation in science and medicine which will be the underlying theme of the Seventh International Congress.

CAUSATION OF CANCER

A special number of the *British Medical Bulletin* has been issued by the British Council devoted exclusively to the causation of cancer.[1] It includes 27 contributions from sixteen different cancer research centres. A similar special number of the *B.M.B.* appeared in 1947, and was concerned chiefly with chemical carcinogenesis. Professor A. Haddow, F.R.S., in his introduction compares these two cancer surveys and points out that the period 1947 to 1958 has witnessed a revival of interest in tumour immunology, with considerable and unexpected advances in our understanding of transplantation immunity and immunogenetics. The nature of the autonomy of tumours and their hormonal dependence has also been much clarified during the last few years and much more is now known about endocrine carcinogenesis.

The advent of the nuclear age has not only brought startling scientific advances, but has also created innumerable problems of hazard and control, many of which have a direct bearing on the incidence of cancer. These secondary consequences of scientific research are refererd to more than once, but considered most fully by Dr. W. M. Court-Brown. After discussing the incidence of leukaemia among survivors of atomic explosions, and among radiologists and patients irradiated for diagnostic or therapeutic purposes, the author summarizes his conclusions as follows:

"The findings of the Atomic Bomb Casualty Commission, the results of surveys on the incidence of leukaemia in irradiated patients, and the increased leukaemia mortality recorded among radiologists, all suggest that ionizing radiations can cause leukaemia in man. Difficulties in interpretation have arisen in some of these investigations, but if all are taken together the data provide convincing evidence of man's susceptibility to the induction of leukaemia by irradiation. It now seems established that radiations do not increase the incidence of chronic lymphatic leukaemia but that they increase the incidence of the acute leukaemias and of chronic myeloid leukaemia. There is some conflict of evidence, in regard to the average length of the latent period, between the Japanese data and the findings of both the spondylitic and Danish surveys. It seems reasonable, however, to conclude that in Western Europe the latent period before the appearance of the acute types of leukaemia is usually from three to five years, but that it may well be longer in some cases of chronic myeloid leukaemia."

The carcinogenic effect of radiation and the manner of its operation are discussed also in papers contributed by Dr. R. H. Mole and Dr. A. Glücksmann, but most of the articles in this special number of the *Bulletin* are concerned with chemical carcinogenesis, and of them the most comprehensive is Professor Haddow's. His masterly survey of a very complex subject ends by pointing

[1] *Brit. med. Bull.*, 1958, **14**, No. 2.
[2] Green, H. N., *Brit. med. J.*, 1954, **2**, 1374.

out that, whatever the precise chemical mechanism of the action of carcinogens, there can be little doubt of the importance of their combination with genetical material or its precursors. It seems at present as if the primary step in carcinogenesis may be the inhibition of certain fundamental processes of genetical or enzyme synthesis.

The papers of chief clinical interest are those on cancer of the bladder contributed by Dr. Georgiana Bonser and her co-workers at Leeds and by Professor E. Boyland, of the Chester Beatty Research Institute. Occupational cancer is discussed by Dr. M. W. Goldblatt, and aromatic amines by Drs. A. L. Walpole and M. H. C. Williams. Both these papers condense much new and valuable information into a few pages.

The article by Professor J. W. Orr which is listed on the cover under the rather misleading title of "Irreversible Changes in Chemical Carcinogenesis" is really a plea for the renewed study of a much neglected subject —namely, the effect of a carcinogenic agent on the nutrient stroma by which a tumour is supported. It is more than twenty years since Orr pointed out that in the case of epidermal tumours there is a progressive alteration of collagen and elastic fibres throughout the latent period which follows the application of a carcinogenic agent, and that the rate at which this change advances is correlated with the potency of the carcinogen used. His subsequent series of grafting experiments has certainly given support to the view that the effects of a carcinogen on the supporting tissues are of first importance.

Many cancer research workers will be glad to have the opportunity of rereading Professor H. N. Green's article on the immunological basis of carcinogenesis, because the theory on which it is based has been considerably expanded and to some extent modified since first published in this *Journal* four years ago.[2] Dr. F. Bielschowsky, of Otago University Medical School, New Zealand, and Professor E. S. Horning, of the Chester Beatty Research Institute, have collaborated in a general review of the influence of endocrines in the development and control of tumours; this is a carefully documented paper with a long list of references.

The "Causation of Cancer" is a subject which looms large in the programme of the International Congress being held in London next week (see leading article at p. 35), though, understandably, no opening speaker has dared to choose it as the title for a communication. From the programme of the Congress it seems most likely that the general subject of the causation of cancer will be a central theme in the discussion of the Biology Sections on Monday and Tuesday afternoon, at the Congress Plenary Session on Thursday afternoon, and in the Biochemistry Section on Friday afternoon, but in one form or another the general aetiology of cancer will form part of the programme of the Experimental Group at each of the morning sessions also.

HEALTH SERVICE EXPERIMENTS

Of all the criticisms of the administration of the National Health Service lack of co-ordination is the one most regularly repeated. Time and time again the various branches of the Service have been urged to work more closely together, yet glaring instances of failure to co-operate are always in evidence. Often these are not the fault of individuals but rather of the system, and it has been one of the important functions of the Nuffield Provincial Hospitals Trust to diagnose organizational defects in the N.H.S. and to see how they can be put right. The Trust's most recent report,[1] published this week, mentions with particular satisfaction the development in the new town of Harlow of comprehensive medical services on which the Trust is spending over £250,000. Co-ordination of services has always been the principal aim of the Trust, and at Harlow "the administration of the various medical and dental services is a divided responsibility, but the whole appears as one service to the patient, because the (group practice and clinic) centres are properly planned and equipped to this end and encourage those working there to co-operate naturally."

One of the most useful services which the Trust, as an unofficial body, can perform is to take unproved but promising ideas and base practical experiments upon them. The report is full of accounts of such experimental studies in all branches of the N.H.S., clinical and administrative. For instance, many patients leave hospital still needing help, and the effect of bringing all the available social services to their aid is being studied; the whole problem of bringing a new hospital (the Princess Margaret Hospital at Swindon) into use is being investigated; the incidence of leukaemia in adults is to be surveyed; the rehabilitation of elderly invalids has been successfully carried out in their own homes instead of in hospital; and a general practitioner is collecting sociological and medical data about his patients with a view to correlating morbidity with as many of the known environmental and hereditary factors as can be obtained.

Some of the most rewarding of the Trust's activities are in the field of mental health. The taking over by a regional hospital board of a home established by the Trust for deaf children with emotional difficulties is yet another example of a successful social experiment by a voluntary body being adopted officially by the State. Another regional hospital board, with the help of a grant from the Trust, has established a "day hospital service" in an ordinary hospital for mental defectives. The patients are brought to the hospital for the day and "absorbed into the hospital routine." The relief to the relatives of the patients is great, and the scheme also helps to avoid the blocking of much-needed beds by long-stay cases. A plan to ease pressure on mental hospitals is being tried out in Worthing, where a district mental health service has been set up. The object of this experiment is to see if a comprehensive psychiatric out-patient service can materially affect the steady annual increase of patients admitted to mental hospitals. Another way of relieving pressure on the hospitals is to see whether some of the long-stay psychotic patients can be improved to the point where life outside the hospital becomes a possibility. The report of the Trust suggests

[1] The Nuffield Provincial Hospitals Trust. *A Record of the Progress of Schemes and Descriptions of New Projects, 1955-1958: Fourth Report*, 1958. Oxford.

that "under certain conditions the mentally ill patient will react to such accepted stimuli from the outside world as incentives." A grant has therefore been made towards the establishment of a work-therapy unit in the grounds of a mental hospital. Here patients will work side by side with normal people in a simple series of manufacturing processes, and they will have the same incentives as are offered to other workers. This is an experiment which will be watched with special interest.

HAZARDS FROM COSMETICS

The incidence of reactions to cosmetics is probably very low, but cannot be accurately assessed. Most women experiencing some irritation or discomfort after using a particular product will change to another without consulting a doctor. Only if the symptoms are severe or prolonged or appear to be provoked by the products of more than one manufacturer is medical advice likely to be sought. Most reactions to modern cosmetics result from the development of a simple allergic sensitivity or from the action of certain ingredients as photosensitizers. Accumulated experience and controlled trials enable manufacturers to avoid incorporating in their products chemicals which are known to be potential sensitizers.

Advances in cosmetic science are often followed by the introduction of new chemicals into cosmetic products. Despite the manufacturers' precautions, untoward reactions, sometimes of bizarre or unexpected pattern, may occasionally be provoked. Recent examples are granulomatous papules in the axillae after the use of deodorant sticks containing sodium zirconium lactate,[1] and dermatitis of the hands apparently caused by the synergistic action of household detergents and triethanolamine in a hand lotion.[2] Such special hazards are rare and can be eliminated once their existence and cause have been satisfactorily established. It may fairly be claimed that cosmetics employed for the purpose for which they are intended provoke reactions in only a very small proportion of users, and that these reactions seldom cause more than temporary discomfort and inconvenience, though they may present the dermatologist with intricate problems in differential diagnosis.

A recent report to the Committee on Cosmetics of the American Medical Association[3] discusses the dangers arising from the misuse of cosmetics. Review of over 15,000 reports of poisoning due to the accidental ingestion of chemicals showed that cosmetics were involved in 3% of cases. Nail lacquers and polish removers, shampoos, permanent-waving solutions and neutralizers, scents, and various lotions were most frequently implicated. Whether cosmetics are responsible for a similar percentage of cases of accidental poisoning in Great Britain is unknown. Deaths from accidental poisoning in England and Wales are classified according to the toxic agent involved and not according to the substance in which the agent was present. However, the Registrar-General has been able to trace since 1950 records of two fatal cases of poisoning in girls under 5 in which a hair lotion was specifically mentioned. The American report draws attention to the increasing use of pharmacologically active substances in cosmetics; even the more conventional ingredients include petroleum distillates, metallic salts, and a multitude of organic chemicals. That manufacturers of cosmetics are aware of the need to consider the consequences of possible misuse is certain; potassium bromate was widely employed to neutralize cold-waving solutions (salts of thioglycollic acid). Since fatal cases of poisoning[4] have been reported less toxic substances have largely replaced bromates.

[1] Sheard, C., Cormia, F. E., Atkinson, S. C., and Worthington, E. L., *J. Amer. med. Ass.*, 1957, **164**, 1085.
[2] Thyresson, N., Lodin, A., and Nilzen, A., *Acta derm.-venereol. (Stockh.)*, 1956, **36**, 355.
[3] Conley, B. E., *J. Amer. med. Ass.*, 1958, **166**, 638.
[4] Dunsky, I., *Amer. J. Dis. Child.*, 1947, **74**, 730.

CONGENITAL DISLOCATION OF THE HIP

From the time of Hippocrates, who associated congenital dislocation of the hip with uterine pressure or birth trauma, various opinions have been advanced to account for the abnormality. The emphasis on environmental factors at the beginning of the present century later gave way to genetical hypotheses; to-day it is thought that both factors play a part and that actual dislocation and subluxation are generally secondary to the more common condition of flat socket associated with genetic dysplasia of the hip.[1] The average age at which the dislocation becomes complete is not known, but usually the femoral head is only partly dislocated during infancy and before weight bearing.[2] Most cases in this country are diagnosed at the age of 1 or 2 years; the earlier the diagnosis is made the better are the results of treatment. A recent paper by R. G. Record and J. H. Edwards,[3] of the department of social medicine at Birmingham University, provides a useful objective analysis of some environmental factors which, they suggest, may be associated with the 186 cases of the abnormality studied in that city. The incidence (0.65 per thousand live births) is low compared with other estimates, but the sex ratio (85% female), the preponderance of left-sided dislocation (64%), and the association with breech deliveries is in conformity with previous reports. The birth weight of affected babies was found to be below the expected figures, and the incidence in the winter was double that in the summer months. The risk of the condition occurring in subsequent pregnancies was about 5%, but this figure naturally depended on the sex and season of birth. Record and Edwards suggest that the seasonal incidence may be associated with the heavier clothing and wrappings used during the cold winter months with a consequent restriction of limb movements, and that similar mechanical factors may be associated with the high incidence of the abnormality among some Lapp and Red Indian communities. This is a controversial hypothesis, but any possible aetiological factor which may be subject to control requires careful study. The Birmingham report as a whole underlines the opportunities for further research into environmental factors associated with congenital abnormalities.

[1] Hart, V. L., *Minn. Med.*, 1947, **30**, 889.
[2] Hindenach, J. C. R., *Lancet*, 1955, **1**, 15.
[3] Record, R. G., and Edwards, J. H., *Brit. J. prev. soc. Med.*, 1958, **12**, 8.

ENUMERATION OF THE "CRAVINGS" OF SOME PREGNANT WOMEN

BY

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The strong desires experienced by pregnant women for various items of food, and even for inedible substances, seem to be a matter of common knowledge, but there is considerable disagreement about the reasons for, and the significance of, these "cravings." It is sometimes stated—for example, by Drummond and Wilbraham (1939)—that a pregnant woman's increased requirement of vitamin C and calcium leads her to crave foods which are rich in these substances; but it is also thought that her desires may be purely psychological in origin. Thus Yudkin (1956) suggests that "the pregnant woman may well demand not oranges but peaches out of season." A search of the literature has revealed only meagre factual information on the subject, and the object of this paper is to describe a collection of such "cravings"—an inadequate record from many points of view, but one which may serve as a stimulus to a more systematic inquiry.

The Records

Early in 1956, during one of a series of broadcasts under the title "Is There a Doctor in the House?" given in the Light Programme of the B.B.C., pregnancy was discussed briefly, and the phenomenon of strong desires for, and aversions from, certain items of food was mentioned. Listeners were invited to write to the B.B.C. on this subject, and the letters received in response to this request have been made available through the kindness of Miss I. D. Benzie, who produced the series.

The nature of the records is such that they do not provide a statistically adequate sample. In the first place, it seems likely to be biased on the side of the unusual, since correspondents to the B.B.C. may tend to write only when there is something remarkable to write about. Secondly, the sample cannot be assumed to be random or representative, since it might be biased both geographically and by the broadcast which gave rise to the letters. Conclusions may therefore be drawn only with caution, and cannot be applied to pregnant women in general; but where a number of women, however unrepresentative they may be, agree in "craving" the same substances to the exclusion of others, some explanation is necessary, though it may of course be psychological rather than physiological.

Results

There were 514 letters, of which 509, reporting 820 pregnancies, have been used in the present report. The remaining five described likes and dislikes for colours, types of music, etc. Most of the letters came from the Home Counties, 102 of the cases reported being in London. There were 36 from Yorkshire, 36 from Lancashire, 23 from Scotland, 20 from Wales, and 1 from Northern Ireland. Most of the reported cases were in 1955 and 1956, but there were many recollected from earlier years, the earliest being in 1894.

The 991 cases of "cravings" have been classified in Table I, which shows the frequency with which various groups of substances were desired. The grouping of substances was decided on as convenient, and it was also considered advisable to separate the records of demands for vegetables and cereal products, according to whether they were eaten raw or cooked, because of the high frequency of the former. By cooked (prepared) cereal products is meant bread, biscuits, cakes, and breakfast foods, whereas a considerable number of the demands were specifically for such foods as macaroni, Indian corn, rice, oatmeal, and maize, eaten dry and raw.

TABLE I.—*Reported Frequency of Cravings Among 991 Cases*

Fruit (see Table II) ..	261	Alcoholic drinks ..	17
Vegetables (raw 72, cooked 33)	105	Ice-cream and iced lollies	17
Confectionery	79	Spices and condiments (eaten neat)	17
Pickled foods	66	Milk and milk products	15
Cereal products (prepared 17, dry raw 48)	65	Sugar and preserves ..	12
Fish (including shellfish)	49	Eggs	10
Nuts	35	Other food products* ..	17
Mineral waters	20	Non-food substances (see Table III)	187
Meat and meat products	19		

*Coffee grounds (5); fat (unspecified) (3); tea leaves (2); aspirin, coconut milk, custard powder, dog biscuits, "health salts," jelly, and "stomach powder" (one each).

In view of the large number of cases of cravings for fruit, these are shown in greater detail in Table II. It is noteworthy that most of those craving apples wanted green sour ones.

TABLE II.—*Details of 261 Cravings for Fruit*

Apples ..	76	Tomatoes ..	31	Pineapples ..	4
Oranges ..	68	Soft fruit ..	25	Bananas ..	3
Other citrus fruits ..	24	Stone fruit ..	16	Dates ..	3
		Pears ..	5	Other fruit* ..	6

*Melon (2), plantains, pomegranates, raisins, and rhubarb.

The frequency of desires for substances normally considered inedible is shown in Table III, and the 193 reports of substances normally liked, but disliked during pregnancy, are detailed in Table IV.

TABLE III.—*Details of 187 Cravings for Substances Other Than Food*

Coal ..	35	Petrol ..	10	Soil	7
Soap ..	17	Polish (metal)	10	Chalk ..	4
Disinfectant	15	Tar	10	Charcoal ..	4
Toothpaste ..	14	Paraffin ..	9	Cinders ..	4
Mothballs ..	10	Wood ..	8	Others ..	30

TABLE IV.—*Details of 193 Reports of Substances Normally Liked, But Disliked During Pregnancy*

Tea	78	Bacon ..	7	Beer ..	4
Tobacco (smoking)	24	Chocolate ..	6	Fish	4
Coffee ..	22	Eggs ..	5	Oranges ..	4
Marmalade ..	8	Sweet foods	5	Others ..	26

There are also certain features common to a sufficient number of the letters to make them worthy of note, though in each case the writer volunteered the information, so that their number is no indication of incidence.

Many correspondents stated that, though they were able to joke about a "craving" after the baby was born, at the time it was overpowering. There are many statements of the specificity of the desire, and there are several descriptions of the temptation to steal in order to satisfy a particular appetite. Though the tone of many letters is amused as well as amusing, written after the event, there is general agreement about the seriousness of these "cravings" during pregnancy.

Also mentioned on numerous occasions is the sense of secrecy which surrounds the phenomenon. Many women state that they went to great lengths to keep their "cravings" secret even from their husbands. Several experienced a sense of shame.

There is no mention in any of the letters of a "craving" not being satisfied. Though there are many descriptions of how the required substance was obtained there are no reports of failure to obtain it. A few state that the satisfaction of their particular demands was capable of unbalancing the family budget.

The stage of pregnancy at which the "craving" was experienced is mentioned in 135 of the letters. Only six state that it was experienced for the full term; 59 report that it was experienced from the first to the fourth month of pregnancy; and generally it seems that the desire is usually felt fairly early.

"Cravings" for two or more substances during the same pregnancy are mentioned in 76 of the reported instances. These have been examined separately for the food items but exhibit no pattern, either of similar or of contrasted substances being craved at the same time. Apart from following the general pattern of Table I they are fairly randomly distributed.

There are 57 cases of the same substance being craved in each of several pregnancies by the same person. Of these, 15 are for fruit and 11 for inedible substances, the others being scattered amongst various foods in too random a fashion to exhibit a pattern or to be reported in detail.

Discussion

The word "craving" commonly applied to this phenomenon may be an unfortunate one. It indicates desire of the strongest possible intensity, and it can be argued that ordinary preferences or likings for various foodstuffs have been called "cravings" in retrospect, the phenomenon being dismissed as due largely to this effect. On the evidence of the present letters there can, however, be little doubt that these desires are real, though it is possible that on occasion they are complicated by the intrusion of ordinary likes and dislikes.

Dietary surveys of groups of pregnant women—for example, People's League of Health (1942) and Burke *et al.* (1943)—make no mention of such large quantities of certain items of food as must have been consumed if these letters are any guide. Whether this is because of infrequent occurrence it is hard to say, but the impression left by the letters is that the women themselves surround their desires with such an aura of secrecy that they may well be more common than the evidence from ordinary dietary surveys would lead one to expect. Also relevant in this connexion, though by no means conclusive, is the total number of letters received. It is, of course, impossible to estimate the proportion of pregnant women who experience these "cravings," but we understand from the B.B.C. that the response rate was striking in view of the casual nature of the request for information, made at a time when the Light Programme is faced with the massive competition of Children's Hour.

In assessing the results of the present inquiry the large number of "cravings" for inedible substances must be largely discounted because of the possibility of bias in favour of the unusual, though many of the items shown in Table III lend support to psychopathic explanations. The preponderance of coal may be due to its having been mentioned by one of the speakers in the broadcast that gave rise to the letters. It was also apparent in many cases that it was the smell of such substances as disinfectant and petrol that appealed during pregnancy; but so many letters were vague on this point that separate results for eating and smelling have not been quoted.

So far as food items are concerned there is no doubt about the preponderance of fruit. Further, some 70% of the recorded cases are for varieties of fruit available virtually all the year round—apples, oranges, tomatoes, and lemons. Availability seems to be a more reasonable explanation of the order of popularity shown in Table II than vitamin C content, though with the exception of apples the more popular fruits are reasonably good sources of this vitamin. Such substances as wall-plaster and chalk are also said to be common objects of "cravings" during pregnancy because of increased requirements of calcium, but the number of such cases recorded in this series is very small.

A more probable explanation is that the expectant mother takes light refreshing snacks of those substances which "go down well" in order to counter the sickness and nausea which often accompany pregnancy, and fruit may be an ideal substance from this point of view. Another is that the snacks may be occasioned by the need for more calories during pregnancy—a general hunger which would hardly justify the use of the term "craving." But why in this case are the "cravings" so specific?

A theory advanced by one correspondent who had gathered considerable information on her own account was that the desire is for something to crunch. The texture of the food, she states, is more important than the flavour. This theory, which was also mentioned in the original broadcast, certainly finds some support in the present data in the high frequency of pickled foods, confectionery, nuts, such unusual foods as dry raw cereals, and the preference for uncooked vegetables.

Clearly, the data are inadequate to prove or disprove any of these hypotheses. They indicate, however, that these "cravings" are real, that they are kept secret so far as is possible, and that there seems to be a preponderance of "cravings" for fruit. Few solutions have been obtained to the many problems which arise in this connexion, but these results may help to pose them in such a way that they could be unravelled by a more systematic inquiry.

Summary

A series of 991 cases of "cravings," and 193 cases of aversions during pregnancy is reported from a collection of letters received by the B.B.C.

A preponderance of the "cravings" for food items was for available fruit, with a relatively high incidence of desires for raw vegetables, confectionery, pickles, and raw cereals. In addition, 187 cases of desires for inedible substances are detailed, the most popular item being coal.

It was clear from the letters that genuine cases of serious "cravings" did occur, and that there was a compulsion on the part of the women themselves to keep their desires secret, which may explain the lack of evidence in published reports of dietary surveys among pregnant women.

ADDENDUM.—Since these findings were reported to the Nutrition Society in May, 1957, our attention has been drawn to a paper by L. B. Posner, C. M. McCottry, and A. C. Posner (*Obstet. and Gynec.*, 1957, **9**, 270) which describes a more systematic inquiry carried out at the Harlem Hospital, New York, where 600 patients in the third trimester of pregnancy were asked, "Is there some special food you crave during this pregnancy?" 394 answered "Yes," 196 answered "No," and 10 admitted "pica." The most common of the 30 items craved were Argo starch (106 cases), sweets (68 cases), and fruit (47 cases). Also noticed were a desire for secrecy and a predominance of "foods commonly found in the average home kitchen." The paper also gives further references.

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WORLD CONGRESS OF GASTRO-ENTEROLOGY

[FROM A SPECIAL CORRESPONDENT]

A World Congress of Gastroenterology was held in Washington during the last week of May. It represented the third international congress of gastroenterology, the first having been held in Brussels in 1935, the second in Paris in 1937, while the third was to have been held in London in 1940 but was prevented by other international events. This first World Congress amply demonstrated the growth of gastroenterology as a special field in medicine, for it was attended by more than 1,100 delegates from fifty different countries. The American Gastroenterological Association was the official host organization.

The programme was a busy one, comprising five main symposia and a very large number of individual communications. The proceedings will fill a large book (to be published in about six months), and even a brief conspectus of the congress cannot be expected from a single pen. I shall confine myself to some of the more interesting points which emerged in the symposia.

Peptic Ulcers

Dr. REINHOLD BOLLER (Vienna) described the medical treatment of duodenal ulcer in his hospital, emphasizing the rapid rehabilitation now being achieved chiefly through the education of the patient in diet, nutrition, and regular habits of living. For gastric ulcers he used a special milk, consisting of "yoghourt" made poor and acid by the use of liquorice, but enriched with fat, and which was known in Austria as "lakhurt." Both duodenal and gastric ulcers were increasing in incidence in Austria, but the loss of work due to them was diminishing with these treatments.

Dr. J. M. DE LA VEGA (Mexico) described sharp differences in the clinical behaviour of peptic ulcer in Mexico compared with the United States. Dr. F. AVERY JONES (London) described studies which had shown duodenal ulcer to be common in all social classes in Great Britain, although those holding responsible positions were somewhat more likely to suffer from it than others. By contrast, gastric ulcer was more prone to affect labouring classes than professional workers. A controlled study had shown that patients advised to give up smoking showed improved healing of a gastric ulcer compared with those who were not so advised; the best results were obtained in those who followed the advice and actually ceased to smoke. Dr. SARA M. JORDAN (Boston, Massachusetts) stated that 10% of the population of the United States suffered from a peptic ulcer at some time in their lives, there being 3.5 men for every woman affected. She estimated the mortality of the disease as 4%, but remarked that the morbidity was great and was very detrimental to the economic life of the nation, especially as the condition was particularly prone to affect men in responsible and executive positions.

Dr. A. LAMBLING and his colleagues (Paris, France) reported interesting features of peptic ulcer in France. At the beginning of this century gastric ulcer in women was the prevalent type of peptic ulcer. Up to 1939 the disease then steadily became more and more represented by duodenal ulcer in men. During the war the disease reverted to the characteristics of a half-century earlier, while since the end of the war it had gradually swung back to the features shown in 1939. The wartime shift was attributed to the emotional shock of the Occupation, coupled with a sudden change in nutritional habits, but not to under-nutrition of itself. Alcoholism did not appear to play any significant role in France. Drs. G. GARRIDO-KLINGE and LUIS R. PENA (Lima, Peru) described the high incidence of gastroduodenal ulcer among miners working in the Peruvian Andes at an altitude of more than 12,000 ft. (3,660 m.). Among these miners, gastric ulcer was many times more common than duodenal ulcer and haemorrhage was a frequent complication. They concluded that vascular changes played an important role in this liability to gastric ulcer at high altitudes. Other speakers dealt with peptic ulcer in Venezuela, India, and Brazil. The discussion was notable for an excellent summing up by Dr. MORTON GROSSMAN (Los Angeles).

Malabsorption Syndromes

Special interest attached to the symposium on this subject, because it is a field of gastroenterology which has shown great progress during the past decade, and especially since the announcement in 1950 by Dicke, of Holland, that removal of the gluten from the diet of children with coeliac disease would bring about normal growth and development. In addition, quantitative methods of studying intestinal absorption have been greatly developed and widely used, while recently biopsy of the small intestine by means of tubes introduced through the mouth has enlightened us on pathology.

Dr. E. E. WOLLAEGER (Rochester, Minnesota) described the behaviour of non-tropical sprue in the United States, emphasizing the fact that impairment of absorption was not confined to fats but applied to all nutrients, including proteins, carbohydrates, vitamins, minerals, and even water. Its diagnosis rested on the demonstration of defective absorption coupled with the exclusion of diseases which might give rise to a secondary steatorrhoea.

Dr. H. A. WEIJERS (Utrecht, Netherlands) described work done in collaboration with Dr. J. H. VAN DE KAMER on coeliac disease and wheat sensitivity, a communication of great interest, as they were pioneers in this field following Dicke's original clinical observations. As well as the generally accepted criteria for making the diagnosis, the establishment of wheat sensitivity must also be shown before idiopathic coeliac disease could be regarded as proved. The existence of such sensitivity could be established by measuring the amount of fat in the faeces after introducing wheat into the diet, but could be established more rapidly by determining the rise of blood glutamine following ingestion of gliadin. In normal people there was little rise in blood glutamine levels, whereas patients with coeliac disease showed a rise of more than 40% with a peak two hours after ingestion. The abnormal increase in blood glutamine suggested that there was defective proteolysis in the intestinal cells.

Dr. MARGOT SHINER (London) described the histological findings in non-tropical sprue as judged from small biopsy specimens obtained by peroral intubation (of which she was the pioneer). There was atrophy of the intestinal villi together with partial atrophy of the crypts of Lieberkühn. The post-gastrectomy and pancreatic types of steatorrhoea did not show any abnormality of the mucosa. In tropical sprue changes resembling those of non-tropical sprue might be found, but they were reversible with treatment with folic acid and antibiotics. By contrast, in patients with non-tropical sprue (idiopathic steatorrhoea) there was no improvement in the histological picture even though the patient had shown complete symptomatic recovery with appropriate treatment. Later in the symposium, Drs. C. E. BUTTERWORTH and E. PEREZ-SANTIAGO (Washington, D.C.) reported somewhat similar histological changes in tropical sprue to those observed by Dr. Shiner. They based their remarks on specimens obtained by means of a very ingenious instrument devised by Dr. W. H. CROSBY (Washington) consisting of a capsule at the end of a fine polythene tube, the capsule being swallowed by the subject. (This instrument seems likely to become a standard research tool, and possibly even a routine diagnostic one. When the capsule has reached a suitable place in the small intestine, suction applied to the free end of the polythene tube causes a knuckle of mucosa to enter a hole in the side of the capsule; this is followed by the creation of negative pressure, which in turn causes the release of a spring-loaded knife which cuts off the knuckle of mucosa. The polythene tube is then used to withdraw the capsule.)

Dr. J. M. FRENCH (Birmingham, England) described the successful results obtained from treating adult cases of non-tropical sprue (idiopathic steatorrhoea) with a gluten-free diet. "Almost all patients respond if appropriate measures are taken." The most important point to realize was the very slow nature of the response in some patients, so that it was necessary to persist with the gluten-free diet for three to six months before abandoning it as useless.

Professor A. C. FRAZER (Birmingham, England) discussed the pathogenesis of the malabsorption syndrome. He recognized two main classes of patient. There were those without intestinal disease who were chiefly examples of lack of pancreatic enzymes, with consequent failure to digest food efficiently. The others had intestinal disease and could be divided into examples of gluten-induced enteropathy (coeliac disease or non-tropical sprue), folic acid deficiency (which dominated some cases of tropical sprue),

altered bacterial flora (which applied in some of the other patients with tropical sprue), enteropathy due to dietary factors such as the ingestion of rancid fats, or one of the diseases in which the bowel wall was grossly abnormal, such as regional ileitis, Whipple's disease, gastro-colic fistula, and "blind-loop" syndromes.

Tropical sprue was dealt with by Dr. F. HERNANDEZ MORALES (Santurce, Puerto Rico), who described both florid and larval forms of the condition, the former being less common now than formerly because of the use of liver extracts and, later, of folic acid and vitamin B_{12}.

Amoebiasis

Amoebiasis remains one of the most important diseases in the world, and the session at the Congress showed how many problems of its epidemiology and treatment remain to be solved. Thus Dr. R. ARMAZ CRUZ reported work from Santiago, Chile, based on the study of 700 cases of intestinal amoebiasis in which the diagnosis was supported by both clinical and parasitological findings. Therapeutic trials had been carried out which gave the astonishing result that a placebo had been found to give a 70% cure rate, whereas some drugs widely used in treating amoebiasis gave results which were no better or even worse.

Dr. ELSDON-DEW (Durban, South Africa) discussed the factors influencing the pathogenicity of *Entamoeba histolytica*, and showed that the mere presence of the organism was not sufficient to cause the disease. The accessory factors were probably complex, and several might need to operate simultaneously to evoke the disease.

In the subsequent discussion Dr. Armaz Cruz's results evoked a good deal of critical comment, especially in view of the fact that a majority of his patients carried "small-strain" amoebae, which some parasitologists consider to be non-pathogenic.

Cancer of the Stomach

Cancer of the stomach remains common in almost all countries of the world, although varying greatly in incidence from one to another, with Japan holding the doubtful distinction of having the highest level. The results of treatment are still disappointing, and there is great need to improve early diagnosis as well as to learn the reasons for the geographical variations in its incidence, which presumably reflect important environmental factors concerned with the aetiology of the condition.

Dr. JOHANNES CLEMMESEN (Copenhagen, Denmark) gave the results obtained by the Danish Cancer Registry for the period 1943–53 and compared the findings with those of other countries. In Denmark, gastric carcinoma accounted for 30% of all cases of cancer, which was somewhat higher than in England, but lower than in the other Scandinavian countries. Gastric cancer was particularly prone to affect the lowest-income groups in Denmark, as was also true for England. On the other hand, the condition was scarce in Africa, so specific carcinogens might be involved.

Dr. LEO RIGLER (Los Angeles, California) considered that detection of gastric cancer was best achieved by *x*-ray examination. It was essential to diagnose the condition early, which could sometimes be done before the stage of symptoms. Routine radiological surveys of the entire population were not practicable, but they were feasible in subjects who were known to be unduly likely to develop gastric cancer. These were patients aged 50 and more with pernicious anaemia, gastric ulcer, gastric symptoms, achlorhydria, or occult blood in the stools. In 3,150 patients with either pernicious anaemia or simple achlorhydria he had found 36 examples of cancer and 80 of gastric polyps, which were known to be pre-malignant lesions. By contrast, not a single example of either cancer or polyp was found in a control group of 1,098 patients with normal gastric acidity.

Dr. I. S. RAVDIN (Philadelphia, Pennsylvania) dealt with the factors affecting the outcome after surgery for gastric cancer. The essential was to diagnose cases while the disease was still limited to the gastric wall. All patients with a gastric ulcer which did not heal in 3–5 weeks with medical treatment should be treated by partial gastrectomy, and it should be appreciated that *x*-ray evidence of healing could not be taken as absolute evidence that the lesion was a benign one.

Nutrition and the Liver

The generally accepted view that nutritional deficiency is of great importance in causing chronic liver disease received some setbacks from some of the information presented. Dr. J. CAROLI and his colleagues (Paris, France) described the close relationship they had found between the average daily consumption of alcohol and the development of cirrhosis. Below 72 grammes of alcohol a day (equivalent to 1 litre of wine) no evidence of cirrhosis occurred. Above 144 grammes, almost all subjects developed hepatic cirrhosis. In between these two limits about 40% of patients were cirrhotic, and it was in this group alone that protein intake appeared to have any influence on liability to cirrhosis. Dr. CHARLES S. DAVIDSON (Boston, Massachusetts), also dealing with alcoholic cirrhosis, considered that the development of this type of cirrhosis was chiefly due to the replacement of normal components of a good diet by alcohol, but he judged that this explanation did not entirely account for the facts.

DRS. BERNARDO SEPULVEDA and SALVADOR ZUBIRON (Mexico City) described their findings in patients with chronic primary malnutrition in whom the total calorie intake had been less than 50% of that usually recommended for health and with low protein and vitamin components. Fatty infiltration was the only hepatic lesion commonly found and cirrhosis occurred only as a rare event.

A Special Social Occasion

One evening of the congress was designated "Embassy Night," to permit foreign delegates and their ladies to attend the embassies of their respective countries. The British contingent was warmly received by HER MAJESTY'S AMBASSADOR and LADY CACCIA, and it may not be amiss to put on record our thanks for the pleasant hospitality they afforded us.

"IN ARDUIS FIDELIS"

SIR GORDON GORDON-TAYLOR'S ORATION

A fine moment in the celebrations attending the Royal Army Medical Corps's diamond jubilee last week was the commemorative oration* Sir GORDON GORDON-TAYLOR delivered in the Great Hall of B.M.A. House on June 25. It was a noble and moving address, not least remarkable for being given without benefit of a single note, entirely from memory. In a way rare in these days, the orator was imbued with the spirit of his subject and complete master of his words.

Mr. WELDON WATTS, President of the Association, welcomed the distinguished and representative audience, and introduced the orator. Mr. Watts recalled that officers of the B.M.A. had headed the deputation to Lord Lansdowne in 1898 to urge the formation of the Corps. "The Association feels reason to be proud in the formation of the R.A.M.C.," said Mr. Watts. "Since its formation it has proceeded from strength to strength."

A Time to Take Stock

"Like Proteus of old, I have assumed many guises," began Sir Gordon Gordon-Taylor. He might even, he said, be

*The oration will be published in full in the *Journal of the Royal Army Medical Corps*.

arraigned for divided Service loyalties. From the well-ironed silk hat and morning coat of the first decade of the century, he had donned the khaki of the Corps, subsequently transferring to the blue and gold of the Senior Service in the second armageddon, and thereafter to the drab and sombre *tenue de ville* of the modern civilian surgeon. "1898–1958: sixty years on!" continued Sir Gordon. "The chariot wheels of time roll relentlessly onward: *omnia fert aetas, animum quoque*—time carries everything away, even the memories. Yet would I dare to challenge the last fragment of this sad Virgilian line. Although we are assured by Sir Thomas Browne that 'diaturnity is a dream and folly of expression,' that is surely but a long-term reflection. Look closer! With each revolution of time's wheels 'who runs may read' on flying felly the impress, perhaps faint, of some event or happening from the past in the life of individual, cohort, corps, nation, or the very world itself. It is fitting that from time to time we should look back and take stock of ourselves: for 'people will not look forward to posterity, who never look backward to their ancestors.'"

It might not to-day be wise to dwell too much on the birth-pangs attending the inauguration of the Corps, the struggle with the War Office and governmental circles. Nevertheless there was one aspect which must be emphasized—the important part played by the British Medical Association, which finally, on January 20, 1898, sent a powerful deputation to wait on Lord Lansdowne, then Secretary of State for War. The deputation was introduced by Dr. Robert Farquharson, himself a former Army medical officer and at that time M.P. for West Aberdeenshire; it included the president-elect of the B.M.A., Sir Thomas Grainger Stewart, who also represented his own University of Edinburgh, and others, as well as the most important officers of the Association. In just two months' time the *British Medical Journal* was able to report "some very satisfactory announcements" from a parliamentary debate. There followed Lord Lansdowne's speech at the mayoral banquet in the City of London on May 4, in which he stated that there would be a new Army Medical Corps and that Queen Victoria had been pleased to signify her intention of bestowing upon it the title "Royal."

Ancestors of the R.A.M.C.

Thirty-six years ago, in his rectorial address to the "red gowns" of St. Andrews University, Sir James Barrie had asked how some old graduate returning to his *alma mater* would spend his time if this were restricted to a single hour, or, better still, with whom would he choose to have a few minutes' conversation. "Many of your Army medical ancestors are far beyond our ken this afternoon," continued Sir Gordon. "John of Arderne, who accompanied Edward III at Crécy in 1346; Thomas Morstede with Henry V at Agincourt in 1415; Gale and Clowes; Woodall and Wiseman." He would like to meet Sir Stuart Threipland, who was Prince Charles's chief medical adviser in "the forty-five," but he would rather talk to Sir John Pringle, one of the founders of modern military medicine. "I should find it difficult to break off conversation with those great surgeons of the Peninsula and Waterloo—Sir James McGrigor, Guthrie, or Hennen." If statuary, obelisks, or eponymous buildings were a talisman to ensure immortality, McGrigor stood secure for all time. A hundred years had passed since his death: sired by an Aberdeen father, he was born at his mother's paternal home in Inverness-shire in 1771. Much of his education took place in Aberdeen, but he also studied medicine in Edinburgh, walking the hundred-odd miles to the Scottish capital and visiting St. Andrews on the way. While deputy inspector of hospitals in the Southern Command, he had to make arrangements for the battered remnants of Sir John Moore's forces from Corunna; finally in January, 1812, at the request of Wellington he arrived in Lisbon to undertake the medical care of the troops. McGrigor wrote of his officers: "Great experience and reflection had at this time created a body of operators never excelled or before equalled in the British Army." He was Director-General from 1815 until 1851.

Hennen died at a relatively early age at Gibraltar of an epidemic fever he was endeavouring to control. George James Guthrie had always been one of Sir Gordon's heroes. He was posted to the 29th Regiment when only 16 years of age, serving with it in North America and the Peninsula. Later, after Waterloo, he successfully amputated at the hip-joint—on a French soldier. This was only the second occasion on which success had attended a British surgeon performing such an operation, the other being by another Army surgeon, Mr. Brownrigg, in 1812. For 30 years Guthrie lectured and gave demonstrations to officers of the Army, Navy, and East India Company without price, as a mark of the esteem in which he held them. He was president of the College in 1833, 1841, and 1854; and he refused a knighthood—"a great little man."

High up on the façade of the London School of Hygiene and Tropical Medicine were carved in stone the names, among others, of Edmund Alexander Parkes (1819–76), an Army surgeon who founded the science of hygiene; David Bruce and William Leishman, both members of the Corps; and Ronald Ross from an allied service. At another place one might see the names of two others who had worked in the Corps—Sir Almroth Wright and Sir Alexander Fleming.

"If services to humanity are the standard of a man's greatness, Whitby stands high among the great benefactors of mankind." One need only reflect on that great Army Blood Transfusion Organization of the 1939–45 war years, which he inaugurated, developed, administered, and commanded, an organization for which more than three-quarters of a million donations of blood were collected; which not only supplied our own armies but also some of the armies of our allies; which created and trained almost a corps of expert transfusion and resuscitation officers. Since some 10% of all wounded men required transfusion fluids, Sir Lionel's contribution to victory was very considerable.

Many would remember Cuthbert Wallace and what he did to advance the surgery of abdominal wounds of war. He saw the importance of early surgery and used to take up Spencer Wells forceps surreptitiously in his pockets. In Mesopotamia George Grey Turner was consulting surgeon at Amara; one of the greatest surgeons of the century, he was an early worker in thoracic surgery. The two surgeons who contributed most to promoting the surgery of thoracic wounds in the 1914–18 war were George Gask and Pierre Duval, of France. More brilliant but only just spreading his wings for his upward flight in chest surgery was Tudor Edwards. And Sir Gordon mentioned many others by name.

Laurel and Rosemary

"The cavalcade has passed," continued Sir Gordon. "The stage is blacked out. We are translated from the past to the fierce light of the present, with eyes firmly fixed on the future with all its incertitude." Remembrance was the greatest incentive and inspiration that history could offer to those who laboured in similar causes to-day. It was unnecessary to go back to Pericles and the Athenian dead; there were memorials nearer at hand, in the R.A.M.C.'s own historical museum at Crookham. "*In arduis fidelis*"—fidelity, next to courage, was the loveliest virtue which God handed down to his children. "I offer to the Corps laurel for tribute on this its diamond jubilee, and rosemary for remembrance of those who have preceded us on the way," concluded Sir Gordon. "*Surgat gloria usque astra.*"

The vote of thanks to Sir Gordon was proposed by the Chairman of Council of the B.M.A., Dr. S. WAND. Sir ALEXANDER DRUMMOND, Director-General, Army Medical Services, then ended the proceedings by reading a message of congratulations to the Corps from Queen Elizabeth the Queen Mother, its Colonel-in-Chief. Before the lecture the R.A.M.C. band was playing in the forecourt of B.M.A. House as the guests assembled.

BRITISH EMPIRE CANCER CAMPAIGN

THIRTY-FIFTH ANNUAL REPORT

The British Empire Cancer Campaign held its annual meeting at the House of Lords on July 1, under the chairmanship of the DUKE OF DEVONSHIRE. Last year the Campaign achieved the record income of £762,972, a rise of nearly £200,000 over the previous year. Of this large sum it spent £620,722 on what are termed "the main objects of the Campaign"—for instance, grants to research centres (£403,000) and individuals (£99,000), fellowships (nearly £29,000), and the installation of a theratron at the Westminster Hospital (£60,000); nearly £60,000 on publicity and appeals; and just over £10,000 on management and administration. The Campaign's income was derived as follows: from donations, collections, etc., £532,000; from legacies, £187,000; from interest on investments, about £44,000.

The *Annual Report* this year is issued in three parts: Part I—"The Chairman's Statement and the Accounts" (pp. i–xl); Part II—"The Scientific Report" (pp. xliii–lxiii and 1–528); and Supplement to Part II—Report by Dr. Percy Stocks on "Cancer in North Wales and Liverpool Region" (pp. 1–156). The *Annual Report* may be obtained from the Campaign's Offices, 11, Grosvenor Crescent, Hyde Park Corner, London, S.W.1.

Progress of Research

The scientific volume opens with this cautiously optimistic appraisal of current research:

"In the field of chemical and physical carcinogenesis, it is not perhaps surprising that the already long list of carcinogens continues to expand. What is more important is that this is matched by a gradual increase in our knowledge of the underlying mechanisms of cancer production, and of the essential differences (especially in biochemical and biophysical terms) between cancer cells and normal cells. Of much current interest are reports of differences in the chemical and physical structure of the cell surfaces, and in the resultant biological behaviour. The newer ideas and methods in immunology also continue to be applied to good purpose. These are among the more rational approaches. Yet there are many other avenues of attack, some of them much more empirical, which cannot be neglected. In the field of experimental chemotherapy, some work is of negative value in serving to define the limitations of individual agents. Equally obvious, however, is that the potentialities in this direction have scarcely been revealed, let alone exhausted."

Here it is possible to note only a selection of the researches reported.

Further work has been done on the identification of polycyclic hydrocarbons in cigarette smoke tar, some of which are known to be carcinogenic. On the other hand, experiments in which animals of many different species have inhaled tobacco smoke for long periods have yielded no tumours. Likewise attempts to produce tumours in animals by skin painting or oral administration of carcinogens from cigarette tar have met with little success. In view of the possibility that 3:4-benzpyrene discharged into the air from motors of various kinds is an additional factor in the causation of lung cancer in cigarette smokers, the effect of combinations of this carcinogen and tobacco condensate on the lung cultures is also being studied.

Besides biochemical and enzymological studies of nucleoproteins, much work is being done on the surface properties of normal and tumour cells.

Endocrinological and Immunological Studies

At several centres work has continued on the elucidation of the endocrine changes in breast cancer patients variously treated by oophorectomy, adrenalectomy, and some form of pituitary ablation. Particular attention has been given to determinations of the oestrogens excreted in the urine, though, states the *Report*, there seems to be little correlation between the results of these and the clinical progress of the patients. An extensive survey of a large series of patients who had in the past been treated with oestrogen has shown that only two out of 530 traced subsequently developed carcinoma, one of the uterus, the other of the breast. Of 120 patients with carcinoma of the body of the uterus, only five were found to have been taking oestrogens for longer than one year some time previously. Other clinical and biochemical studies of the endocrine aspects of breast cancer have included a comparison of the effects of pituitary yttrium implantation with adrenalectomy. Oestrogens continue to be excreted in the urine even where the endocrine ablation is complete.

A judicious, intermittent use of prednisone and prednisolone has been shown to provide a means of controlling adrenal activity in post-pubertal adrenal hyperplasia.

Further studies on cancer immunology are reported. The main lines followed at one centre include the detection of antibodies in tumour-bearing animals and of immunological changes during chemical carcinogenesis. At another centre the immunological structure of normal and carcinogen-treated tissues is being examined to determine whether abnormal tissue antigens are formed during carcinogenesis. Attempts to inhibit carcinogenesis by producing immunological tolerance to cancer tissue formed *in vivo* have been unsuccessful. Studies have also been carried out on the phenomenon of tissue transplantation immunity and on the immunological consequences of inducing tolerance of skin homografts in mice by inoculating them at birth with living adult homologous spleen cells.

Experimental Chemotherapy

A new series of cyto-active amino-acids is being studied, and of special interest is a mannitol-busulphan—the first of a new series of busulphan-like derivatives—of low toxicity yet with powerful tumour-inhibitory properties. In studies of the mechanism of action of alkylating agents, a new lead has arisen from the observation that deoxyguanilic acid can be alkylated *in vitro* at the 7-position of the guanine moiety. This and related work is stated to be of great potential interest as suggesting the possible importance of alkylation of the purine moieties of nucleic acid in the production of biological effects.

Twenty-one new nitrogen-mustards have been synthesized, designed to act selectively on tumours by enzymic action at the site or by selective transport.

Clinical Studies

With increasing experience of exfoliative cytology in the diagnosis of malignant disease of the uterus it is being found at most centres that three or four women out of every 1,000 attending gynaecological clinics have unexpected cancer of the cervix, usually carcinoma *in situ*. At one centre, however, the incidence of pelvic malignancy revealed by cytology when no clinical suspicion attaches to either the history or the clinical findings is put as high as 2%.

Two investigations bearing on the surgery of carcinoma of the bronchus are reported, one designed to discover for how long the blood supply of the lungs can be interrupted without permanent loss of lung function, the other to establish the precise routes of direct spread of these tumours. Fourteen pregnant patients treated with radium for cancer of the cervix have been reviewed to determine the influence of pregnancy on the clinical course of the disease after treatment.

The incidence of structural damage in the chromosomes of tumour cells of experimental animals has also been studied, more especially in relation to the influence of oxygen tension on the effectiveness of a given *x*-ray exposure. An extensive investigation into the important question of the reduction in life span and the acceleration of ageing by ionizing radiation has been started at one centre, and the effects of radiation and radiomimetic chemicals on ageing have been compared at another centre. The effects of radiation on many different aspects of iron metabolism in experimental animals are also being investigated.

Natural Radioactivity

The measurement of the low levels of radioactivity which occur in our natural environment continues to occupy an important place in the study of factors which may influence cancer incidence. On the physical side such measurements

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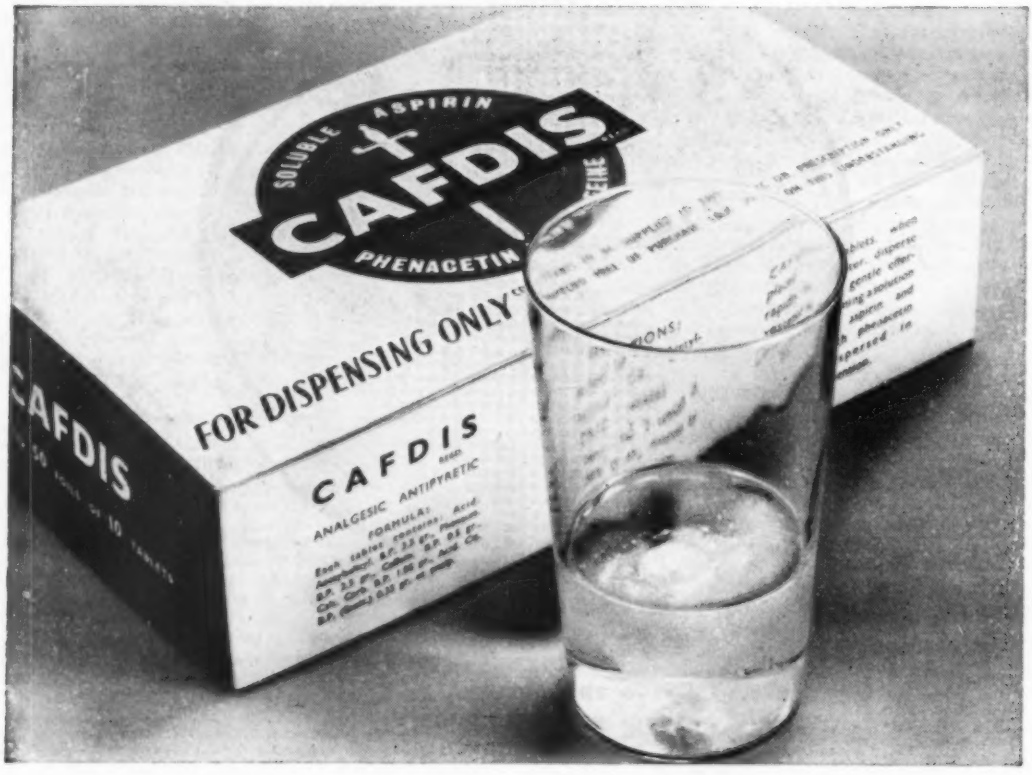

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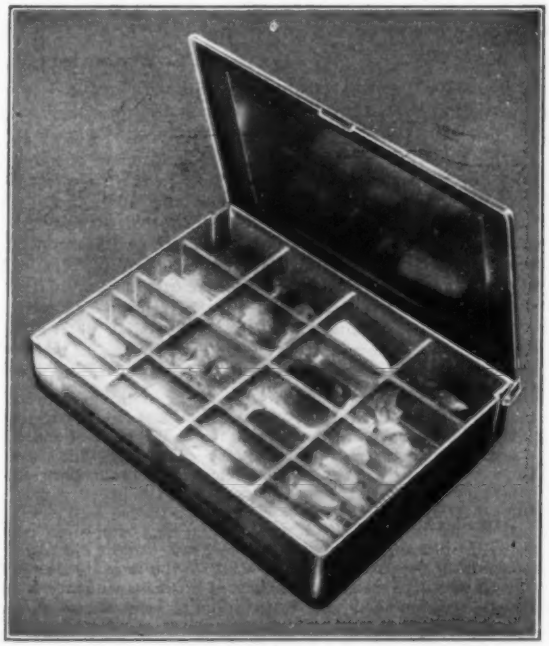
make the highest demands on technical development. This year has seen important advances in assay procedures for trace amounts of alpha, beta, and gamma ray emitters, states the *Report*. "A very beautiful technique for the measurement of alpha ray activity, which combines extreme sensitivity with comparative simplicity, has enabled measurements to be made of the total alpha ray emission from radioactive atoms present in small samples of the human skeleton, and to apportion the activity roughly between members of the radium and thorium series." The examination of 20 skeletons from different parts of the country has shown that, although there are some differences with geographical situation, there is very little correlation between concentration and the age of the subject. Even foetal material generally shows relatively high concentrations of radioactivity. This part of the Campaign's programme includes a study of the metabolism of some of the more hazardous isotopes, such as ^{90}Sr, and of methods of removing them from wastes by ion-exchange processes.

For the purpose of identifying and measuring the body content of gamma-ray-emitting isotopes, a large cylindrical plastic scintillator has been found to offer a good compromise between the high sensitivity but low resolution of liquid scintillators and the good energy resolution but moderate sensitivity of sodium iodide crystals. For regional surveys of environmental gamma radiation, portable high-pressure ionization chambers have been developed with which doses of one microroentgen can be measured to an accuracy of a few per cent. in three minutes.

New Appliances

A PESSARY RECOGNITION BOX

Mr. C. H. DE BOER, assistant gynaecological surgeon, United Liverpool Hospitals, writes: Patients complaining of recurrent vaginal discharge frequently give a history of past treatment by drugs in the form of pessaries. Often an



identification by shape and colour can be made by the patient. Through the courtesy of Messrs. Ward Blenkinsop & Co. I have obtained a demonstration case for the pessaries commonly used in this area and have found it most helpful. By its use the repetition of ineffective treatments can be avoided.

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Dindevan (Evans Medical Supplies Ltd.).—This is phenindione, an anticoagulant which exerts its effect by interfering with the hepatic synthesis of prothrombin. Its chemical formula is related to that of dicoumarol (or bishydroxycoumarin). It is more rapidly absorbed than dicoumarol and exerts its full effect clinically 24 to 36 hours after treatment is started. Its duration of action is shorter, and prothrombin activity returns to normal within 48 to 72 hours after treatment is stopped. In addition its effects on blood coagulation are believed to be more constant, and hence the dose is more uniform. It is supplied in tablets containing 10 mg. and 50 mg. The tablets are given orally, 200 mg. on the first day, followed by 50 mg. twice daily, the exact dose for the individual patient being carefully controlled by daily prothrombin estimations. Treatment is aimed at increasing the blood prothrombin time to two to three times normal. When given for long periods, smaller doses are prescribed and prothrombin estimations are less frequent.

Phenindione is given for the treatment of coronary thrombosis, phlebothrombosis, and pulmonary or peripheral embolism. The use of this or similar anticoagulants has helped to reduce the incidence of serious post-operative thrombo-embolic complications. Its place in the treatment of coronary thrombosis is still a matter of controversy, though clinical evidence is mounting to show that it helps to prevent the spread of thrombosis locally in the coronary vessels and to prevent the development of thrombosis elsewhere, especially in the calf veins with consequent pulmonary emboli. The possibility of serious complications in the form of severe haemorrhage must be set against this, and some clinicians feel that the dangers outweigh the therapeutic advantages. It is generally thought, however, that phenindione is indicated in the more severe cases of coronary thrombosis, though it is doubtful whether it need be given in the milder cases. The drug is contraindicated in severe hepatic or renal disease and also in peptic ulcer or haemorrhagic disease on account of the danger of serious haemorrhage. Vitamin K_1 should always be available to combat the complication of haemorrhage; 10 to 20 mg. intravenously or 20 to 25 mg. orally will reverse its action and produce a rapid fall in prothrombin time in 6 to 8 hours.

N.H.S. basic price: 100 10-mg. tabs., 15s.; 100 50-mg. tabs., 21s. 8d.

Rondase (Evans Medical Supplies Ltd.).—This preparation of the enzyme hyaluronidase is supplied in ampoules containing 1,500 international units in freeze-dried powder. Water or normal saline must be added to it before use. The solution is compatible with most fluids given by subcutaneous injection. In a dose of 1,500 units the drug has no side-effects.

The essential action of rondase, as of other preparations of hyaluronidase, is to aid the dispersal of fluids injected into the tissues. By this means it aids the penetration of local anaesthetics, but at the same time it hastens their absorption and thus tends to increase their toxicity. Hyaluronidase may also be added to solutions used for hypodermoclysis, but the need for this procedure is limited. Hyaluronidase has a reputation for dispersing irritant substances injected accidentally paravenously. Thus it can be employed to diminish the likelihood of local reactions to thiopentone or the contrast media used in radiology when they escape outside a vein.

It has been suggested that hyaluronidase may be injected into areas of oedema with a local cause, but this measure, though rational therapeutics, is not firmly established.

N.H.S. basic price: 6 ampoules, 14s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Alcohol and Driving

SIR,—I was interested in the article by Professor John Cohen, Mr. E. J. Dearnaley, and Mr. C. E. M. Hansel, "The Risk Taken in Driving Under the Influence of Alcohol" (*Journal*, June 21, p. 1438). However, I wish to suggest that the authors have drawn a very false conclusion in their penultimate paragraph, when they write "either a large number of people are wrongly convicted by the magistrates or wrongly acquitted by the jury." Electing trial by jury usually involves a counsel's brief and is a costly affair. It would appear fairly logical that people with a good defence should resort to such a tactic and those without a reasonable answer to the charge should content themselves with a magistrates' court, which in the event of conviction tends to be more lenient.—I am, etc.,

Chirk, North Wales. R. P. W. KUP.

SIR,—The publicity that the article by Professor John Cohen, Mr. E. J. Dearnaley, and Mr. C. E. M. Hansel on "The Risk Taken in Driving Under the Influence of Alcohol" (*Journal*, June 21, p. 1438) has received in the press, and the legal implications of such articles, invites enlargement and comment.

The ability to drive after the consumption of alcohol must be related to the initial level of competence of the driver, and it would be only reasonable to test the offender's ability to drive the vehicle concerned whilst sober before deciding that his incompetence was due to the effects of alcohol. Many of us have been granted licences to drive vehicles whose dimensions may be similar to that of a Manchester Corporation bus after having passed a test on a vehicle three feet (0.9 m.) narrower and a tenth the weight. It would have been interesting to have included a control group of, for example, university staff who hold licences to drive heavy vehicles but who have not actually passed a driving test on such a vehicle and who do not drive one regularly.

The gap through which the drivers who had taken 6 fl. oz. (170 ml.) of whisky could drive was only 0.6 in. (1.5 cm.) less than that through which the control group could drive, a difference of 0.6% of the total width of the gap. This is a figure which would hardly seem significant, even statistically, and the number of drivers who took part in the tests is not stated.

It is a pity that the convivial atmosphere which is said to have been present when the tests were commenced was not extended to those who undertook the test sober, and they were not subsequently invited to take the test after the consumption of alcohol. It is possible, as the method of selection of the controls is not stated, that those who cautiously avoided taking the test after the consumption of alcohol were by nature also the more cautious drivers, so that the results of the experiment might have been reversed if they had been given the alcohol and those who were audacious enough to consume 6 fl. oz. (170 ml.) of whisky before driving a bus had been persuaded to take the test sober. They might then have been able to show off their natural audacity by even greater overestimation of their ability to drive a bus through a narrow opening. It would have been more enlightening if each driver had acted as his own control, and half had been tested before alcohol and the other half had been tested whilst under the influence.—I am, etc.,

Altrincham, Cheshire. J. F. PATRICK.

Prevention of Lung Cancer

SIR,—The letter from Dr. Lennox Johnston (*Journal*, June 21, p. 1483) raises issues that are even more important than his main theme, serious as the problems of lung cancer and excessive smoking may be. Since I do not smoke, Dr. Johnston will perhaps exonerate my remarks of the hypocrisy that he associates with those who do.

Dr. Johnston will surely not expect his unrealistic scheme for curing the nation's smoking almost overnight to be taken very seriously. I hope, also, that he does not really mean what he writes about the propriety of deliberately frightening people. There are extremely cogent objections to the practice of frightening children about the effects of fire or anything else. It is essential to protect young children from fire and other dangers by external means over which, like Legge's workmen, they have no control. This must continue until they are mature enough either to assess the dangers realistically for themselves or to be reliably obedient to parents with whom they have a sufficiently trusting relationship (which is the more likely if, *inter alia*, the parents have not deliberately frightened them). Guiding a child into habits of safety, and explaining the reasons for these, is of course quite a different matter from frightening the child (or the smoker) as Dr. Johnston advocates.

Foolhardy behaviour of either children or adults, in common with many other psychological difficulties, is ultimately a result of some kind of fear, and it often appears to be caused by fear of the consequences of the very activity in question. Perhaps, therefore, the resistance of some smokers to repeated warnings is due, not to a hypothetical process of immunization, but to a compulsive need for reassurance that the danger is not after all as serious as the warnings assert. If this be so, a campaign to induce greater fear seems rather futile. The motives of smokers (and also the motives of those who are anxious to prevent smoking) are undoubtedly complex, and clearly the problem can have no such simple solution as that proposed by Dr. Johnston. In general medicine it has long been recognized that rational therapy demands an understanding of underlying processes and is not achieved by merely trying to abolish symptoms. It is also generally agreed that the adequate physical care of children is a much better way to produce healthy adults than trying to correct maldevelopments in later years. Unfortunately there is still considerable resistance against accepting that these principles are just as true for psychological problems—amongst which smoking must surely be considered one of the less important.—I am, etc.,

St. Albans, Herts. A. C. WOODMANSEY.

Cancer Education

SIR,—The efforts of Mr. Malcolm Donaldson to promote wider dissemination of what we know to be the true picture of cancer have aroused the gratitude and admiration of many of us, so that his letter in the *Journal* of May 31 (p. 1302) deserves support. The reluctance in this country especially to accept information about cancer, or even to acknowledge its very existence, is more reminiscent of the ostrich than of beings endowed with perception and judgment. Surely it is time for the psychologist to enter this field as he has done so effectively in other spheres of public relations where irrational factors seem to be operating.

Many people regard a malignant growth as something with an independent life which is devouring them and which cannot possibly be brought under control, so that a diagnosis of cancer is necessarily a sentence of inevitable mutilation, pain, and eventual destruction. It is no use telling them either collectively or individually that they are wrong and that it is better to diagnose cancer at an early stage when it can be treated with a very good chance of palliation, if not cure, as they simply do not believe it. It is surely significant that in almost any lay discussion about cancer frequent reference is made to the large number of sufferers who die apparently uninfluenced by treatment, while in a similar discussion about, say, hypertension or heart disease reference is rather made to the increasing number of sufferers living happy and useful lives as a result of treatment.

In some countries, such as France, there is wide publicity of the early signs of cancer, coupled with assurances that treatment gives great hope of cure, but there has not been any significant improvement in the overall survival figures after some years of this propaganda. In this country there is the impression, possibly due to the news value of large benefactions and of large and

impressive machinery, that cancer can only be helped at all by treatment in one of the large centres with "something atomic," as a recent patient has put it, so again there is a denial of the confidence placed in the ordinary facilities provided for medical treatment at provincial level. It seems that the word "cancer" conveys much of the despondency, and just as the gradual substitution of "T.B." for "consumption," with its sinister connotation, has accompanied the change in outlook about this disease, so should we hope to find some new general term to cover the neoplastic diseases.

But, until such time as we can fully control new growth, it can be shown that we have much to offer, and that it is just as possible to live with a tumour as with arthritis.—I am, etc.,

Hove. E. MILLINGTON.

Asphyxia by the Cord

SIR,—I should like to comment on Dr. H. E. Reiss's scholarly and well-documented article on "Foetal Asphyxia Associated with Umbilical Cord Around the Neck" (*Journal*, June 14, p. 1394). I assume that the foetal distress was caused by tension during labour on a relatively short cord and not solely by the number of coils.

At first sight it seems strange that, while cord round the neck is common, foetal distress is rare, but Nature has provided two compensating mechanisms. First, if the length of cord from placenta to neck is very short, the breech presents and will not turn spontaneously. Secondly, Nature provides a push on the fundus by means of the voluntary contractions of the diaphragm and abdominal muscles during the second stage of labour. This helps to relieve tension. It follows that, if the child can survive the squeeze of the uterus, which increases the length of the uterine cavity during the first stage, it ought to be able to survive the push and squeeze of the second stage. Dr. Reiss's case illustrates very clearly that foetal distress appeared during the second stage. When the os is fully dilated it is undoubtedly proper to correct any malposition and deliver with forceps so long as firm fundal pressure is maintained during delivery. Push, and tension is released; pull, and tension is increased. If the cord is intact when the head is delivered, it is always possible to deliver the body by fundal pressure without dividing the cord.

It is a pity that British textbooks accept the findings of Gardiner,[1] as they are demonstrably false. It is untrue to say that a cord of nearly 13 in. (32 cm.) is necessary for spontaneous delivery. Gardiner forgot that the fundus can follow the foetus and be pushed down nearly to the symphysis pubis either by the mother's own efforts or by the obstetrician. Nature provides the human foetus with a very long cord, usually 20 in. (50 cm.) or more, not because it is necessary for delivery—indeed, the longer the cord the more likely it is to become coiled round the foetus and so be relatively short—but because it was necessary for many hundreds of thousands of years for the mother to be able to pick up her child immediately after delivery without tension on the placenta during the hazardous third stage. But that, Sir, is another story.—I am, etc.,

Cambridge. C. W. WALKER.

REFERENCE

[1] Gardiner, J. P., *Surg. Gynec. Obstet.*, 1922, **34**, 252.

SIR,—Cord round the neck is a common condition at birth, and Dr. H. E. Reiss (*Journal*, June 14, p. 1394) rightly points out that it may cause serious foetal asphyxia and even foetal death. Whether or not the foetus shows signs of distress from compression of the umbilical vessels depends, firstly, on the tightness of the cord round the neck, and, secondly, on its thickness. The amount of Wharton's jelly in cords is variable, and, when it is reduced, the umbilical vessels, deprived of its cushioning effect, are more easily compressed.

During an investigation of 100 cases of foetal distress at St. Helier Hospital, Carshalton, several years ago, I attributed 24 of them to cord round the neck. What impressed me most was that signs of distress appeared late in labour. In 20 cases it occurred in the second stage and in the remaining 4 at three-quarters dilatation. I believe that the reason for this is that the cord is liable to be nipped by the foetal chin during flexion and rotation of the head on the pelvic floor. Since delivery can usually be readily effected when the danger signs appear, the baby is saved in most cases and stillbirths from cord round the neck are relatively rare.—I am, etc.,

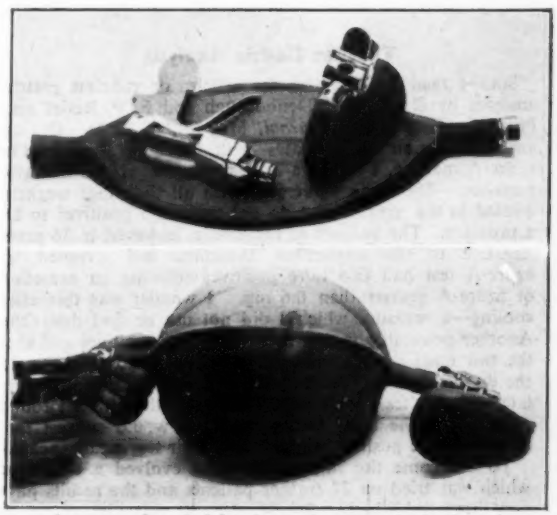
Birmingham, 16. D. B. WHITEHOUSE.

SIR,—I read with interest the article by Dr. H. E. Reiss (*Journal*, June 14, p. 1394), not so much on account of the coiling of the umbilical cord around the foetal neck five times, but because general inhalation anaesthesia was used when it was known foetal distress had been present for some time. It is not surprising there was delay in establishing regular respiration in a baby when, in addition to the distress, a second dose of pethidine, 125 mg., was given two and a half hours before the administration of cyclopropane, gas, oxygen, and ether. Caudal analgesia by the single-dose technique would have been well worth attempting. In the majority of patients it is simple to administer, effective, and always safe to mother and baby. Moreover, it takes little time and one knows well within fifteen minutes if one has been successful. The time to have given it would have been just prior to full dilatation. This would not have delayed, but probably hastened, labour. That the method is a practical one I have proved to myself, and now it is my method of choice in all vertex presentations requiring forceps unless the head is very low, in which case local analgesia is used. In the last 225 cases there have been 25 failures and not all these have failed completely. General inhalation anaesthesia is not only dangerous to the mother but also to the baby, particularly to the latter when there has been evidence of foetal distress.—I am, etc.,

Haywards Heath, Sussex C. J. FARR.

Out-patient Anaesthesia

SIR,—Professor William W. Mushin and Dr. Peter W. Thompson's favourable report (*Journal*, June 14, p. 1376) on cyclopropane in out-patient anaesthesia may help to persuade manufacturers in this country to make the necessary apparatus. More than two and a half years ago I



Apparatus for administering cyclopropane in dentistry.

developed in conjunction with Sparklets Ltd. the apparatus shown in the photograph; but it was not put into production because the value and safety of this method of anaesthesia did not seem to have gained wide acceptance by

anaesthetists. Cyclopropane continued to be regarded as too powerful and dangerous to be placed in the hands of the "occasional" anaesthetist.

Ever since 1951, when I first described the use in out-patients of 50% cyclopropane given from a six-litre bag,[1] I have urged the safety of the method. The following year I reviewed 1,000 administrations and suggested that it might, with advantage, replace the nitrous oxide method[2]; and in 1954, the year in which Hingson[3] began to use it, I reported nearly 2,000 administrations and repeated my suggestion.[4] Nevertheless, contrary to the statement of Mushin and Thompson, cyclopropane has never been widely tried in out-patient work. Moreover, apart from Hingson and myself, the few who have made reports have used it in low concentrations which give longer and therefore less satisfactory induction and recovery. None of them suggested its general adoption in place of N_2O; only Hingson supported me in this.

In the apparatus shown here, the Sparklet bulbs, which are sealed together, charge the bag through a non-return valve with 50% cyclopropane, and oxygen and nitrogen in equal parts, after which the gun is detached. The mixture is non-ignitable, but, as with Hingson's mixture, if it is discharged from the bag into a flame the cyclopropane will catch fire, since on leaving the bag the gas becomes diluted with air and enters its ignitable range. Warning should also be given that nitrous oxide and oxygen given nasally to dental patients after induction with the cyclopropane mixture, as Mushin and Thompson recommend, may reintroduce the risk of igniting the patient's breath with sparks from teeth and dental forceps.

A soda-lime canister has not been incorporated in the apparatus, because it was designed for use by "occasional" anaesthetists, whom I recommended not to prolong the administration for more than a minute. This gives satisfactory anaesthesia lasting about a minute and a half, which is sufficient in most of the dental-extraction cases that need general anaesthesia, which number more than 2,000,000 a year in England and Wales. The soda-lime canister in Hingson's apparatus gives it a distinct advantage in other kinds of operation, for which more prolonged administrations may be needed. If either type of apparatus were made available, the method might be given the extended trial I have long thought it deserved.

—I am, etc.,

London, S.E.1. J. G. BOURNE.

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1 Bourne, J. G., *Brit. med. J.*, 1951, **1**, 1330.
2 —— *Lancet*, 1952, **2**, 705.
3 Hingson, R. A., *J. Amer. med. Ass.*, 1954, **156**, 604.
4 Bourne, J. G., *Proc. roy. Soc. Med.*, 1954, **47**, 416.

Tubeless Gastric Analysis

SIR,—I read with interest the articles on tubeless gastric analysis by Drs. M. A. Denborough and F. P. Retief and Professor L. J. Witts (*Journal*, May 24, p. 1213). During an investigation of 23 cases with "diagnex," using the azure-A method, I had five false negatives. I had no false positives. This is in agreement with all the other workers quoted in the article, who do not find false positives to be a problem. The authors of the article, however, in 36 cases negative to the augmented histamine test screened by azure-A test had two false positives showing an excretion of azure-A greater than 0.6 mg. I wonder was this after cooling—a measure which I did not use or find desirable. Another possibility is that these were true positives and that the test meal was at fault probably owing to passing into the duodenum. In the one positive I had that did not correlate with the test meal, when I repeated the latter, I found that in fact the meal was at fault. I would suggest that apparent false positives should have their test meal repeated.

To overcome the false negatives I evolved a technique which was tried on 27 further patients and the results have now been published.[1] Briefly, the test was carried out as usual and the urine was tested immediately. If it was negative a gastric tube was passed at once and the gastric contents aspirated. The tube was therefore passed about 2½ hours after the granules had been swallowed. The aspirated juice showed one of three things: (1) The gastric contents were normal in appearance—i.e., the dye had passed through the stomach and it was therefore a true negative. (2) There was a large or small amount of undissolved granules, showing that there was some gastric hold-up with achlorhydria. (3) There was a large amount of partially undissolved granules, this being evidence of gastric hold-up with free hydrochloric acid present.

Using this modification I was able to eliminate the problem of false negatives. It will be evident that in about 70% of cases it is not necessary to pass a gastric tube. Further, an unsuspected delay in gastric emptying may be revealed. I have found the azure-A test, with this modification, to be an excellent one, although it cannot always be strictly called "tubeless."—I am, etc.,

Dublin. TERENCE CHAPMAN.

REFERENCE

1 Chapman, T. T., *J. Irish med. Ass.*, 1958, **42**, 124.

Treatment of Leg Ulcers

SIR,—The following quotation from a letter written in 1781 will interest those doctors who have taken part in the correspondence on the treatment of leg ulcers by compression:

Dear Sir, . . . A gentleman whose leg had been ill for several years and had several running sores on it, was advised by an old Clergyman to discard his physicians and surgeons and to follow this simple prescription: "Take a fillet of soft Welsh flannel four inches broad and four yards long, let it be rolled as *tight* as you can bear it over your leg from the knee to the sole of the foot, and keep it on day and night without any alteration." He wore this for a month and has been perfectly well ever since. If she is not well already, I have little doubt but that the same method would cure Mrs. Brackenbury. I trust that you and she are both pressing on to the mark and strengthening each other's hands in God.

I am, dear sir,
Your affectionate friend and brother,
JOHN WESLEY.

This letter is interesting as showing that wisdom is not confined to us. It was written by the Rev. John Wesley[1] to Robert Carr Brackenbury from Towcester on November 19, 1781.—I am, etc.,

Hong Kong. D. VAUGHAN REES.

REFERENCE

1 *Letters of the Rev. John Wesley*, 1931, vol. 7, p. 90, edited by J. Telford, Standard Edition. Epworth Press, London.

Chain-store Glasses

SIR,—I missed Mr. J. Primrose's letter (*Journal*, April 19, p. 943), but with Mr. A. C. Shuttleworth's (*Journal*, June 14, p. 1419) no medical practitioner, one might think, could disagree. I expressed the same views three years ago (*Journal*, July 23, 1955, p. 267). Yet from time to time I learn from patients that they have been sent by their doctors direct to opticians for examination of their eyes with the object of getting glasses *if thought desirable*, rather than to medical practitioners at hospitals or in the competent Supplementary Ophthalmic Service provided by the State. (To their honour, I have known opticians to resist the temptation to correct the small errors of refraction which are almost invariably present.) If the Ministry is aware of this undesirable practice, it may feel justified in taking appropriate action, and the profession has partly itself to blame for an unwise decision.

But buying glasses over the counter is another matter. Every day I use professionally a pair—the last survivor of half a dozen pairs, the others being war casualties—of multiple-store glasses bought 25 years ago at a shilling a pair. One more breakage, and, if the Opticians Bill is passed, replacement will cost £1 for the lenses and a considerable sum for the frame. Well, that won't break me financially, but it will be a hardship to many poor people who can see just as well with self-chosen 3s. 6d. spectacles (I think that is now the store price) as with the £2 plus ones. Why, then, interfere with a harmless and necessary trade

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which has never been known to damage eyes, and has had the implicit support of such specialists as Sir George Berry and Mr. D. Priestley Smith (*Journal*, August 6, 1955, p. 382). Mr. Shuttleworth does well to appeal for clear thinking and unprejudiced judgment.—I am, etc.,

Portsmouth. W. S. INMAN.

Case of Exomphalos

SIR,—I feel it is worth while reporting a case of exomphalos which survived operation but died on the twenty-third post-operative day with volvulus of the mid-gut.

H. A., a baby boy, was admitted to the Evangelical Hospital on January 1, 1958, at the age of 1 hour, with a congenital umbilical hernia. The liver and parts of the gut were felt in the hernial sac. The baby weighed 2.375 kg.

The baby was prepared for operation when it was 2 hours old, but it was noticed that the colour of the face, hands, and feet was becoming blue and the operation had to be postponed until the baby recovered good colour. It was taken to the theatre at the age of 5 hours. At operation the contents were found to be the liver, many loops of small intestine, caecum, and appendix, together with a part of the transverse colon. The coverings were intimately adherent to the antero-superior aspect of the liver over more than two-thirds of its extent. These were patiently freed, although I had to leave a good deal of the extra-embryonic coelom adherent to the liver, which had to be returned with it to the abdominal cavity. The gall-bladder was peeping through a circular hole on the anterior surface of the liver; it could not be seen on the inferior surface nor was it adherent to the liver substance; it was covered with peritoneum all round. A Meckel's diverticulum was found lying along the small intestines and stuck to its wall with fine adhesions near the terminal ileum; it was about 2 cm. long and 5 mm. wide.

The defect in the abdominal wall measured 7 by 10 cm. This was too small for the reduction of the liver and I had to enlarge the opening upwards to achieve this stage of the operation. Reduction could not be completed without aspirating most of the gas in the intestines at three different points. The wound was closed satisfactorily with difficulty and the baby was sent to its cot on hourly feeds of 10 ml. glucose-water for six hours and then three-hourly feeds of 30 ml. for the rest of the first 24 hours. It was given its mother's breast next morning. It sucked vigorously and thrived well, gaining weight after an initial loss of 250 g.

On the evening of the twenty-third post-operative day the baby suddenly collapsed and became cold and pale. It was screaming all the time, pulled its knees to its abdomen, and vomited repeatedly. The abdomen was slightly distended at first, but it became excessively so in less than three hours. Its condition deteriorated very quickly and the baby died eight hours after the start of symptoms. No post-mortem examination could be done, and the diagnosis of volvulus of the mid-gut is based on the clinical findings alone.—I am, etc.,

Nablus, Jordan. E. HANDAL.

Azacyclonol in Schizophrenia

SIR,—The general conclusion of Dr. S. Gray and Dr. A. D. Forrest (*Journal*, February 15, p. 374) that azacyclonol is "unlikely to be a very useful drug in the treatment of chronic schizophrenia" agrees with my own experience with this drug[1] *in the dosage employed*. I also agree that further trials using higher dosage are indicated. May I, however, question the means by which their conclusions were reached?

In the course of their "controlled trial," 17 out of 40 patients received reserpine, and another 6 chlorpromazine, together with the drug being tested. This means that, in fact, only 17 patients could be expected to demonstrate change attributable to azacyclonol, any alteration in the mental function of the remainder being possibly due to the effect of a *combination of drugs*. That this point is of importance can be demonstrated by the effects of other drugs given in combination. Examples easily come to mind from clinical experience—e.g., potentiation of barbiturate activity seen commonly with some phenothiazine derivatives.

It would seem appropriate to recommend the greatest caution in interpreting the effects of medication on mental function. Research design should attempt to eliminate, so far as possible, any artifact. The objections to attempting to reach conclusions about the activity of any drug when it has been administered in conjunction with another also apply to the administration of psychotherapy during a drug trial or indeed to any change, physical or psychological, in the patient's environment.—I am, etc.,

Williamsburg, Va., U.S.A. BASIL E. ROEBUCK.

REFERENCE

[1] Peak, E. C., Canestrari, R. E., and Roebuck, B. E., *J. nerv. ment. Dis.*, 1956, **124**, 504.

Out-patient Gynaecology

SIR,—Dr. Max B. Clyne (*Journal*, June 7, p. 1353) says, "And yet out of 60 women 42 . . . were referred to the wrong agency . . ."; and earlier, "This is a very serious challenge to us general practitioners." Certainly. Think again. A gynaecological (or any other) department is a consultant department even before it is a specialist treatment department, under the charge of a consultant.

The general practitioner, when in doubt and difficulty, will not institute psychological treatment until he has excluded organic causes for the symptoms. All these 60 women were rightly sent to a consultant, who was able to reply in 42 cases, "There is no gynaecological organic lesion; you may institute your psychological treatment with a clear conscience."—I am, etc.,

Crowthorne, Berks. H. D. FORBES FRASER.

Induction of Labour

SIR,—As a general practitioner who does a fair amount of midwifery, I was very interested in the paper by Mr. Ian Cope and Mr. Morton Pearson (*Journal*, May 24, p. 1211) and in the letter by Professor G. Gordon Lennon and Mr. E. M. Edwards (*Journal*, June 14, p. 1413). I do not wish to enter into the discussion about the thorny question whether such a high induction rate is justified, especially as you dealt with this problem so excellently in your leading article (*Journal*, May 24, p. 1226). However, I wish to express my surprise that neither of the two reports mentions the possibility of medical induction.

For several years now I have made it my rule to induce labour if the patient goes two weeks beyond her expected date, and earlier if there are signs of toxaemia. Lacking facilities of an operating-theatre, I naturally turned to medical induction, and, since an intravenous drip is also difficult to arrange under domiciliary conditions, I adopted the following method.

1. The patient is given 15 mg. stilboestrol every waking hour. This apparently heroic dosage is surprisingly well tolerated by most patients.

2. If labour has not started after about 48 hours, the patient is given a course of oxytocic injections. She is asked to come to the surgery, and is warned that she may have to stay there for 2½ hours, and that she may have to take a taxi to get home. Oxytocin injections are then given at half-hourly intervals, up to six injections if necessary, starting with 0.3 ml., then 0.4 ml., and then for four times 0.5 ml.

3. If after the sixth injection the patient has only slight and indefinite contractions, she is given six 2 gr. (130 mg.) tablets of quinine sulphate, and asked to take one tablet every half-hour, but to stop it if she starts labour, or if she notices any ill effects like palpitations or deafness or buzzing in her ears.

Unfortunately I am unable to give the exact number of cases in which this method of induction was tried, but I can trace the records of 13 cases, and I remember only three failures. Although I realize that these figures are too small to draw any valid conclusions, they do show that it is worth while to try medical induction before one turns to surgical methods.

The advantage of medical induction becomes obvious if one considers that surgical induction is not without dangers and disadvantages. Cope and Pearson mention the increased caesarean-section rate with its increased morbidity rate, and the psychological shock to the patient. They do not mention the (although rare) cases of ruptured uterus in succeeding pregnancies. They mention that the morbidity rate in

the induced cases could be kept low only by the routine use of antibiotics—with all its well-known disadvantages and dangers. Neither of the two reports mentions whether there was an increased forceps rate with its additional risks (anaesthetic) and its psychological shock, and neither of the reports mentions whether owing to the difficulties and complications of dry labour (with or without forceps) there was an increased number of spastic, epileptic, and mentally defective children.

To avoid misunderstanding, I wish to make it clear that I found medical induction ineffective if used to induce labour before term.—I am, etc.,

Leicester. BELA GALANDAUER.

Food Conversion in Babies

SIR,—Dr. Ian G. Wickes's letter (*Journal*, June 14, p. 1415) makes the suggestion that the ratio *weight of food consumed/increase in infant body weight* may produce an index figure useful in diagnosing certain diseases of infancy, a high index suggesting poor food utilization.

It seems probable that a group of healthy infants would be found to have widely varying indices and that any given infant would have a variable index from period to period. The range acceptable as indices within normal limits would therefore have to be broad, and the wider the acceptable normal range the less the value of the index as a diagnostic pointer. However, within the range of normal conversion ratios, the difference in index obtained for a number of healthy infants (healthy, that is, on general clinical grounds) might be attributed to a difference in metabolism, providing the broadest of pointers to the future nature of the individual. A high figure clearly suggests that the baby will become active-minded and highly strung rather than placid and easygoing.

If, in this respect, time showed the ratio to be in any sense reliable, it might be of help to those subsequently endeavouring to assess the child's temperament against a background of data supplied and perhaps coloured unduly by parents or others. The ratio would be comparable with an E.S.R. in being free from external influences but in requiring judicious appraisal of its meaning and worth in the individual case.

Such philosophical studies do not of course interest the farmer in studying the meaning of his pig conversion ratios. To him, high ratios mean only more fodder to provide without financial return, but, since high-ratio infants may produce some of the more talented of our species, we need not take the same gloomy view of them.—I am, etc.,

Nottingham. GORDON CURRIE.

Mortality and Morbidity of Steroid Therapy

SIR,—In a leading article last year[1] you warned us about the mortality and morbidity which follow treatment of arthritis with steroids. Bunim was mentioned as having reported six deaths in 39 patients after prednisone. Of 50 patients of mine who started prednisone treatment more than two years ago,[2] four have died. Others who have reported fatal arthritic cases are Nelson,[3] four; Stolzer *et al.*,[4] three; Hart *et al.*,[5] two; Medical Research Council and Nuffield Foundation,[6] one. Three times as common were non-fatal gastro-intestinal disasters, severe infections, thrombo-embolic episodes, heart failure or arrhythmia, and mental disease.

Previously the mortality and morbidity after cortisone and corticotrophin were equally high. The Americal Rheumatism Association reported 26 deaths in 446 rheumatic patients in one year.[7] Howell and Ragan[8] reported 11 deaths in 68 patients; West[9] 6 deaths in 52 patients, and Savage[10] 6 deaths in 90 patients. The mortality rate for Levin *et al.*[11] was five in 50 patients; for Toone and Irby[12] five in 35; for Bunim *et al.*[13] five in 78; for the Medical Research Council and Nuffield Foundation[6] 2 deaths in 33 patients in one year. Similar death rates were seen in controlled trials on non-fatal disorders such as skin diseases[14] and asthma.[15] Baldwin *et al.*[16] had 7 deaths in 60 steroid treated asthmatic patients. There is a steadily increasing roll of death and disease from this therapy, for which I can see no compensating advantage.—I am, etc.,

East Melbourne, Australia. M. KELLY.

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Full-term Extrauterine Pregnancy

SIR,—Professor Coralie Rendle Short reports a case of a full-term extrauterine pregnancy with a living child, followed two years later by a full-term normal delivery (*Journal*, May 10, p. 1123), and, not having heard of a similar case, she was interested to learn that such a patient could conceive again so easily. The following case provides further evidence that this can happen.

A coloured woman, aged 22, primigravida, was admitted as an emergency to the Provincial Hospital, Port Elizabeth, on April 4, 1951, as a case of "obstructed labour." She was 37 weeks pregnant and had complained of abdominal pains for three days. The pains had increased in severity and she was very distressed on admission. She was small and thin, and her pulse rate was 128 per minute. The abdomen was distended, and the foetus, which was lying obliquely, was easily palpable under the thin abdominal wall. No foetal parts were palpable in the pelvis and the cervix was closed. A provisional diagnosis of an extrauterine pregnancy was made and was confirmed at laparotomy, when a healthy female infant weighing 5 lb. 2 oz. (2.6 kg.) was delivered from the sac. The placenta was firmly attached to the left broad ligament, the small bowel, the mesentery, the transverse colon and mesocolon. The tubes were not identified, as they were obscured by the numerous adhesions. The umbilical cord was cut short and ligated; the sac was closed and the placenta left *in situ*. The mother made a normal recovery and left hospital with the baby on the tenth day.

On August 23, 1953, the patient was again admitted in labour and had a normal vertex delivery of a healthy male infant, weighing 7 lb. 4 oz. (3.6 kg.). The duration of labour was 13 hours. The first child had died at 9 months from bronchopneumonia.

If a patient who has had an extrauterine pregnancy does not return to hospital for her subsequent confinements, the case will almost certainly be lost sight of. I feel sure that somewhere in Africa and Asia there are several of these unrecorded cases which have had subsequent normal deliveries at home.—I am, etc.,

Port Elizabeth, South Africa. G. MAIZELS.

Do Sebaceous Cysts Exist?

SIR,—Would Dr. J. L. Edwards (*Journal*, June 21, p. 1480) then leave us with no difference between our old "seb. cysts" and implantation dermoids except that in the latter condition the causative factor is believed known?—I am, etc.,

Leicester. B. J. FOWLER.

Monkeys for Polio Vaccine

SIR,—I still enjoy a good steak even though I find slaughterhouses revolting. Likewise my whole family have been given poliomyelitis vaccine even though its production depends on the death of many monkeys. However, I could not help feeling that if the word "slave" had been substituted for "monkey" your annotation on monkeys for polio-

myelitis vaccine (*Journal*, May 17, p. 1168) might have appeared in a moderately enlightened early nineteenth-century medical journal.

"Slaves are trapped by professional trappers——Some——will have to be destroyed or released because they are unfit for export. ——a load of healthy slaves will tolerate a journey of many days, with little or no loss in transit. Indeed the slaves' health may improve on the journey owing to their receiving better food than in the wild state. ——The worst of the slaves' hardships occur before they reach the (ship) and this is a matter for the exporting countries to control. ——only large operators can supply the slaves in the numbers in which they are required. ——the supply might be less liable to interruption from political or religious motives. ——The African species are different but would probably serve well enough——."

There seem to be other reasons than mere shortage of supply for hoping that technical methods will be evolved which will obviate the use of monkeys.—I am, etc.,

Fort William, Ontario. P. C. MACGILLIVRAY.

Medical War Crimes

SIR,—I should like to add to the comments made by Dr. Wilhelmina C. Maguire (*Journal*, June 14, p. 1420). The fact that notorious German doctors, tried, found guilty, and heavily sentenced for crimes of unbelievable horror, are now restored to full rights of medical practice in Germany—their sentences reduced, and discharged because of good behaviour—seems beyond belief.

One overwhelming surprise has been the damage still existing among the victims of these experiments. The wounds and results of operation can heal and stay healed apparently, but psychological trauma remains. To see a victim professionally to-day—15 years after—reduced to tears and trembling by the simplest and kindest examination produces an urge to see simple justice done and their needs given careful and practical consideration. Surely Germany must stand by her promises to the United Nations and fulfil her promise to help and compensate such cases. Some victims have been given compensation on a truly absurd financial basis; many have not even had this.

Surely the revelations of a doctor's wife, who herself was an eye-witness, will stir medical men and women to express in no uncertain terms what we in England feel on this subject. To Mrs. Salvesen,[1] wife of the medical adviser to the Norwegian Royal Household, we owe a debt for her book, *Forgive—But Do Not Forget*, for throwing into the limelight the misdeeds of the German medical profession in charge of prison camps in Germany.—I am, etc.,

London, N.W.8. E. T. WRIGHT.

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SIR,—We are asked by Dr. Wilhelmina C. Maguire (*Journal*, June 14, p. 1420) to join her in taking action to prevent war-criminal Dr. Herta Oberheuser from continuing to practise medicine on the grounds of her past behaviour. I wonder if it would not be more adult for Dr. Maguire to present us with the facts as they are now. We might find that this person is now a dedicated practitioner, doing good work. It is possible. If it were so and Dr. Maguire knew it, I wonder if she would be so determined to finish what she wishes to start.—I am, etc.,

Derbyshire. A. P. TAIT.

Tetanus Immunization

SIR,—It is heartening to read the letter (*Journal*, May 17, p. 1176) from the honorary secretary of the Medical Officers of Schools Association deploring the indiscriminate use of anti-tetanus serum in casualty departments and stressing the desirability of boosting active immunization wherever possible. Your leading article on this subject[1] admirably summarizes the strong grounds on which this plea is made.

One must agree, however, with Mr. Maurice Ellis (*Journal*, May 31, p. 1299) that it is usually extremely difficult to obtain information regarding previous active immunizations. In previous reviews on the matter[2 3] I have stressed the need for providing the sort of record that Dr. A. H. Morley issues at Mill Hill School (*Journal*, May 31, p. 1299), and Dr. H. J. Parish's authoritative book[4] makes this necessity quite clear. It has been suggested, so far without avail, that the Medical Directorates of the Armed Services should issue each Service man returning to civilian life with a small card giving a record of his Service immunizations so that the growing pool of actively immunized civilians does not drain away. It would not be impossible to find a space on the National Health Medical Card (Form F.C.4) for this purpose. The Wellcome Foundation have, in fact, issued for some years past a neat and comprehensive record card of protective inoculations, supplied on request, and one would like to see this used in all cases of such prophylaxis.

It is only by means of such a record-card system that the increasing build-up of actively immunized members of the civilian population can be utilized to supersede the less effective and more hazardous method of passive immunization. Dr. Morley's remarks that, in spite of the production by his boys of record-cards, serum has been given to them in casualty departments support my previous contention that the teaching on tetanus immunization in medical schools still leaves very much to be desired.—I am, etc.,

London, S.W.3. NOEL H. MOYNIHAN.

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Guildford Cathedral

SIR,—May I be allowed very warmly to support the appeal by Dr. J. O. M. Rees and others (*Journal*, June 14, p. 1419) on the matter of a window in the name of the new Guildford Cathedral to be given by the doctors? I hope this appeal will be met with a brisk response. As I am a Guildford diocesan lay reader and an honorary guide the issue is one which is very near to my heart. This beautiful cathedral will be undoubtedly one of the twentieth century's most remarkable buildings. When the Queen saw it a year ago she very aptly described it as being so serene and beautiful.

In connexion with the proposed window I feel it would be a splendid idea if a doctor with an artistic gift could design it. As readers of the *Journal* may know, the nurses' window has been designed by a qualified nurse. It might be possible, as with the nurses' window, to hold a competition for the best design. Medical men have a great variety of hobbies and skills apart from their own vocation.—I am, etc.,

Redhill, Surrey. J. B. GURNEY SMITH.

Occupational Diseases of Musicians

SIR,—I am at the moment completing a paper on occupational diseases of musicians. There is very little in either medical or musical literature about this, and the material at my disposal has been obtained partly from my own limited clinical experience in this field and from information volunteered by musician friends. I am anxious to obtain further case histories from doctors who have had experience in treating musicians, and would very much appreciate it if any of your readers who are interested would care to share their experiences with me. The source of this information would of course be acknowledged.—I am, etc.,

Ingham Infirmary, Westoe Road, South Shields. M. ANDERSON.

Obituary

Sir RUDOLPH HAMPDEN SMITH, Bt., C.B.E.
M.B., B.Ch., F.R.C.S.

Sir Rudolph Hampden Smith, honorary consulting surgeon to the Torbay Hospital, died at Hindhead on June 25, aged 89.

Thomas Rudolph Hampden Smith was born on January 24, 1869, the eldest son of Sir Thomas Smith, first baronet, who was consulting surgeon to St. Bartholomew's Hospital, Surgeon Extraordinary to Queen Victoria, and Honorary Sergeant-surgeon to Edward VII. Rudolph Smith was educated at Winchester, Trinity College, Cambridge, and St. Bartholomew's Hospital, qualifying in 1892 and graduating M.B., Ch.B. two years later. He took the F.R.C.S. in 1895. After holding resident appointments at St. Bartholomew's he became a consulting surgeon at Stockton-on-Tees, where he was on the staff of the local hospital. During these early years he wrote a number of papers on surgical subjects, including one published in this *Journal* on "Chloroform Syncope and Direct Manipulation of the Heart." In 1909 he succeeded his father as second baronet, and a few years later he moved to Torquay, where he was appointed to the consulting staff of several hospitals in the locality. During the first world war he directed a hospital for the wounded and was appointed C.B.E. in 1920.

Sir Rudolph married Ann Ellen Sharp in 1897 and she died in 1928. The heir to the title is his nephew, Mr. Thomas Turner Smith, of New Zealand.

Mr. H. K. GRIFFITH writes: During the first world war Sir Rudolph showed that he was an able organizer as commandant of the Torquay Hospital for the wounded, and in 1922 he was appointed honorary secretary of the committee responsible for building the new Torbay Hospital. In this he spared neither time nor energy in working with his colleagues to produce the best possible hospital for the district. The Torbay area owes him a great debt for the work he did so efficiently. An excellent clinician, he was deservedly popular with his colleagues, whom he was always ready to help in any way. With his patients he was sympathetic and inspired complete confidence. He did not suffer fools gladly, and if a house-surgeon did something foolish he was unlikely ever to repeat it. In committee he was a good chairman, and would enliven the proceedings with an occasional witty remark. Like his father he was an excellent raconteur and after-dinner speaker. Among his professional brethren he set a high ethical standard.

OSCAR PARKES, O.B.E., M.B., Ch.B.

Dr. Oscar Parkes, who practised in London and in Ringwood, Hampshire, died suddenly at his home in Co. Down on June 24, aged 72. A well-known naval historian, he was editor of *Jane's Fighting Ships* from 1918 to 1935.

Oscar Parkes was born at Handsworth, Birmingham, on October 18, 1885, the son of Dr. W. E. Parkes. He was educated at Rydal Mount, Colwyn Bay, Berkhamsted, and Birmingham University, where he graduated M.B., Ch.B. in 1914. He played both rugby football and cricket for his university. After holding resident appointments at the General Hospital, Birmingham, he joined the Royal Navy, and towards the end of the first world war served in the Naval Intelligence Division at the Admiralty. In 1919 he became official naval artist and director of the naval photographic section at the Imperial War Museum. Before he left the Service in 1920 he had already been appointed editor of *Jane's Fighting Ships*, an annual publication founded in 1897. Between the wars he practised in Knightsbridge and was for a time an adviser in neurology to the Ministry of Pensions. He moved to Ringwood in 1943 and continued to practise there, being for a time on the staff of Fordingbridge Hospital. Six months ago he retired from medical practice and went to live in Northern Ireland, having been appointed a director of a publishing company there.

Besides his work as editor of *Jane's Fighting Ships*, Dr. Parkes contributed many articles on naval history and other matters to the *Navy League Magazine* and other journals. He was a very capable marine artist and had exhibited at the Royal Academy. His major work, *British Battleships from 1860 to 1950*, was published at the end of last year.

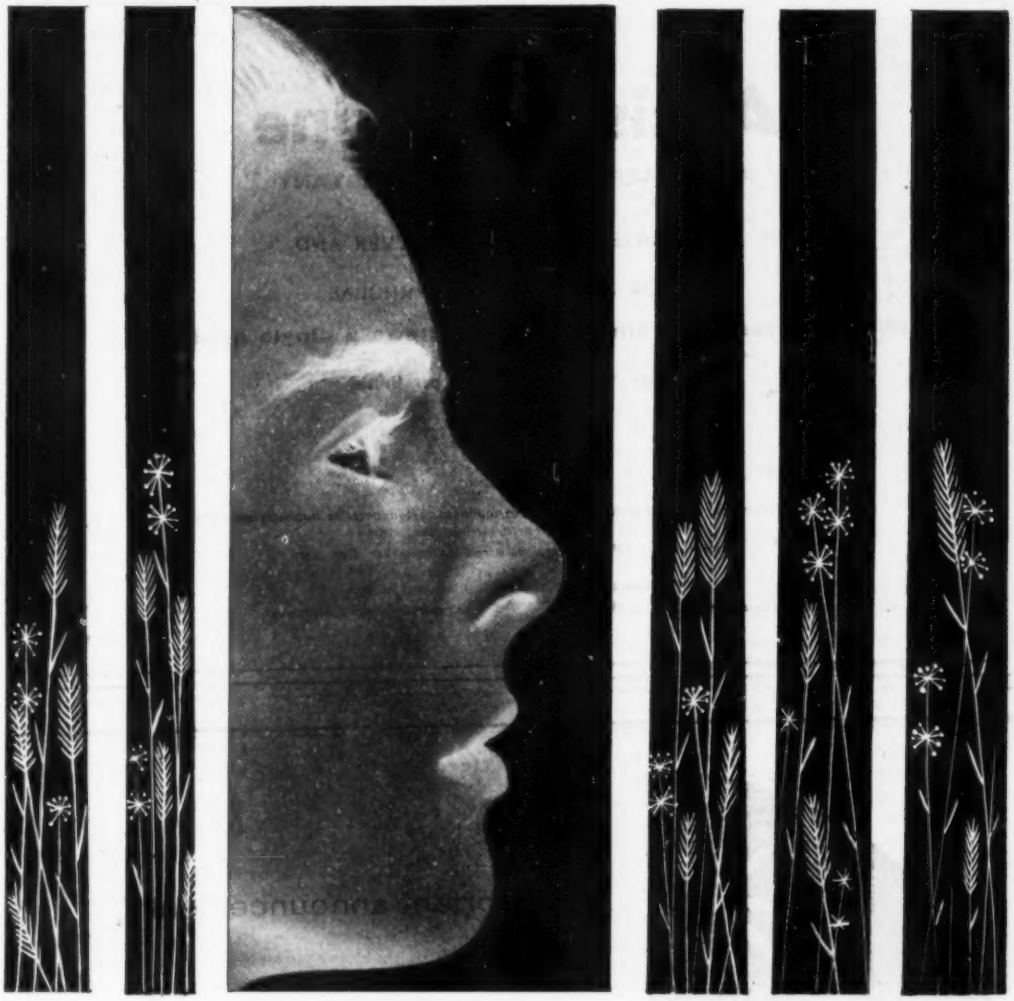
R. H. L. writes: Oscar Parkes came to Ringwood about 1943, when he took over a small general practice. He had previously been in specialist practice in London, and was always ready to admit that general practice was not his *métier*. He continued to follow his previous work in his general practice, and this consisted of electrical treatment of various kinds, in which he had a fanatical faith. He always strongly resented the fact that the National Health Service did not include payment for such services. He was indeed a real "character" in the true sense of the word, always full of fun, kindliness, and energy. But his two chief interests in his leisure hours were his "ships" and his garden. There must be many more capable to tell of his vast knowledge of the Royal Navy, as shown in the fact that for about 17 years he was editor of *Jane's Fighting Ships*. He was a fine artist and very ready to use this gift to entertain others. A founder member of Rotary in Ringwood, he could, with a blackboard and chalk, be always relied on for a most entertaining evening. He retired to Ireland last year when his wife became seriously ill, and she predeceased him by only a very few months. We would like to extend our sympathy to their only child, a daughter, now living in Ireland.

H. M. PEREIRA, L.R.C.P., L.R.C.S.Ed.
L.R.F.P.S., D.P.H.

Dr. H. M. Pereira, formerly smallpox consultant to the Ministry of Health and medical superintendent of the Eastern Hospital, London, died at his home at Bexley, Kent, on June 11. He was 87 years of age.

After qualifying in Scotland in 1895 Henry Manning Pereira held posts in the fever-hospital service in London and then took the certificate of the London School of Tropical Medicine and the D.P.H. of Cambridge University in 1901. Going out to India, he worked first at St. Martha's Hospital, Bangalore, and then became medical officer to tea plantations in Mysore. Coming back to London, he rejoined the fever-hospital service, and after many years in various posts in and around London he was appointed medical superintendent of the Eastern Hospital in 1930.

Dr. J. PICKFORD MARSDEN writes: H. M. Pereira was one of that famous medical team who worked under T. F. Ricketts in the Hospital Ships and River Ambulance Service during the smallpox epidemic of 1900–2. Thereafter he never ceased to practise, and to preach, that great master's teaching on the diagnosis and the hospital management of smallpox. Because of his characteristic modesty, to the medical world at large Pereira was probably the least well known member of that team; but those of us who worked under him learned more about smallpox from him than from any other source. And his value, especially to medical officers of health, as a consultant—a real smallpox expert of the Ricketts school—was, of course, outstanding and almost unique. In addition to his smallpox experience Pereira possessed an exceptional knowledge of diphtheria, enteric fever, and the old type of scarlet fever gained from years of work in the fever hospitals of the Metropolitan Asylums Board; and when the London County Council took over those hospitals in 1930 he was appointed medical superintendent of the Eastern Hospital at Homerton, where he remained until his retirement. Pereira was a most lovable man, supremely happy in his family life. There are many of us who will treasure the memory of his friendship.



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EUNICE M. HATCH, M.R.C.S., L.R.C.P.

Dr. Eunice M. Hatch died suddenly at her home at Palmers Green, London, on May 9. She was 64 years of age.

Eunice Mary Hatch was born in Highgate and studied medicine at the London School of Medicine for Women and at St. Mary's Hospital, where she was one of the first women students. Qualifying in 1927, for some years she was in general practice at Ilford, and later became an assistant in a country practice at Lavington, Wilts. In 1940 she returned to London, where she practised in Wood Green until her death. She will be greatly missed by her patients, who appreciated her unfailing kindness and sympathy and her special gift for allaying their anxieties with her humour and cheerfulness. During the second world war Dr. Hatch gave much valuable help to the Red Cross, in addition to bearing the strain of working during the numerous air raids.—G. P. S.

G. J. WILLIAMS, M.D.

Dr. G. J. Williams, who was a general practitioner in London, died peacefully at his home in Paddington, aged 95.

Dr. E. O. LEWIS writes: Much has been written about the "country" doctor, but comparatively little about the "town" and especially the "metropolitan" doctor. Dr. Griffith Jones Williams may be aptly described as a "country" doctor in a metropolis. At all times, and especially when dealing with patients, Dr. Williams had, and induced in others, that feeling of leisure we associate with rural life. His slow, quiet, and dignified entrance to the sick-room gave the patient a sense of calm and assurance. He always gave the impression that he had plenty of time to listen to his patient, and he was most indulgent towards those who were garrulous and hysterical. Dr. Williams's professional approach to his patients was a great contrast to the hustling visit that the overworked general practitioner these days often finds compelled to do.

The family to which Dr. Williams belonged has rendered great services, more particularly in medicine, to Londoners during this last century. His father, Elias Williams, was a chemist in Poultry, E.C., in the middle years of the nineteenth century—a strong personality who was a pioneer in establishing Welsh Presbyterian churches in the metropolis. Three of Elias Williams's sons became doctors and had separate practices in Paddington. Dr. Isaac Williams, the eldest, after about twenty years in practice died in 1896. The second son, Dr. John Cadwaladr Williams, was nearly fifty years in practice before he retired to North Wales, where he died in 1950; his daughter, Dr. Mabel Rolant Thomas, is a dental surgeon in Caernarvon, and his son, Sir John Cecil-Williams, is the honorary secretary of the Honourable Society of Cymmrodorion. Dr. Griffith Williams was the youngest son of Elias Williams, and he spent the whole of his professional life, with the exception of a few years when he was in Kroonstaad and East Rand, in London. His eldest son, Dr. Howell Griffith Williams, was in practice with him for a few years, but died in 1950 when in the prime of life. This is surely a unique record of medical service in one metropolitan area by one family.

Dr. Griffith Williams received his medical training in Edinburgh, where he graduated M.B., C.M. in 1892, and in 1915 he proceeded to the M.D. All-round efficiency and thoroughness were Dr. Williams's chief features as a clinician. Although he was in practice when past his 90th birthday he kept abreast with modern methods of treatment; but he was critical of the indiscriminate empiricism in the use of some of the synthetic proprietary drugs practised by the younger generation of doctors. During the first world war Dr. Williams gave valuable services as a physician at military hospitals; and during the last war he continued with his general practice in Paddington. He was not absent from London a single night during these six years. The "courteous old doctor" was a familiar figure to the residents and war workers in Paddington, and he was highly respected by them for the great service he rendered in the terrible conditions in London at that period. One night heavy bombs razed to the ground all the houses opposite his surgery and several others on both sides. When the doctor was in one of the top rooms above the surgery an incendiary bomb burst through the ceiling and fell on the bed on which he was resting; he calmly rendered the bomb harmless, removed it to a safe place, and then continued with his rest. Dr. Williams had a most lovable disposition; he was a better saint from his first birth than most Christians are after their "second birth." Even those who lived daily with him never remember Dr. Williams ruffled, annoyed, or irritable. Whilst he had in himself all the resources for contentment, he was very sociable. His geniality, courtesy, and delicate humour made him a most acceptable and congenial member of any home circle, club, or society.

The infirmities of old age which he suffered without complaint compelled Dr. Williams to retire soon after he was 90 years of age. His last years were made as happy and as comfortable as possible by the devoted and excellent nursing care of Mrs. Williams, and the companionship of his only surviving son, Mr. John Trevor Williams. Both have the solace of many happy memories of a most charming personality.

T. R. WILSON, L.R.C.P., L.R.C.S.Ed. L.R.F.P.S.

Dr. T. R. Wilson, who practised for many years at Wainfleet, Lincs, died at Skegness on June 10.

Thomas Robert Wilson studied medicine at Anderson's and St. Mungo's Colleges, Glasgow, and qualified in 1917. After a period of active service in the R.A.M.C. he settled in practice at Wainfleet and became a well-known figure in the medical life of the district.

R. N. K. writes: Dr. Thomas Robert Wilson came to Wainfleet in 1921, bringing with him a pawky sense of humour which was to be enjoyed by his patients and colleagues. He served this community for 33 years and quickly earned the respect and esteem of its members. A firm favourite with children, there were many now grown up who inquired anxiously for their well-remembered "Dr. Thomas" during his last illness. He had seen service with the R.A.M.C. during the first world war in Egypt and Palestine, and was a member of the British Legion. He was a familiar and popular figure at B.M.A. functions and was chairman of the Holland Division in 1950. It was a bitter blow when the illness which overtook him in his last years of practice curtailed his activities. The many who miss him extend their deepest sympathy to his wife and son.

JOHN LAMBERT, O.B.E., M.D., D.P.H.

Dr. John Lambert, who was medical officer to Wellington College for 27 years, died suddenly at Crowthorne, Berkshire, on June 16. He was 78.

John Lambert was born at Sheffield on January 2, 1880. From the Perse School, Cambridge, he won a scholarship to Downing College, and took first-class honours in the Natural Sciences Tripos. Going on to the London Hospital, he graduated M.B., B.Ch. in 1904, proceeding to the M.D. in 1908 and taking the D.P.H. in 1909. After holding the posts of house-surgeon and house-physician at the London Hospital, he became a clinical assistant at the Hospital for Sick Children, Great Ormond Street, thus stimulating his interest in paediatrics. Thereafter he became senior medical officer to the Brighton education committee, and then, for two years, medical officer to Lancing College. Joining the Royal Navy at the beginning of the first world war, he served mainly in hospital ships, and was appointed O.B.E. in 1919.

Leaving the Navy with the rank of surgeon commander in 1919, he went to Wellington College, where he spent the greater part of his life before retiring in 1946. In his work

there as resident medical officer and as doctor to neighbouring preparatory schools he built up a reputation for accurate diagnosis and sound advice on all matters of school health. He acquired a wide experience of the ailments and epidemics of schoolboys, and, though he wrote little for publication, he kept the most careful records of all medical events at Wellington and his other schools. Though retirement brought him relief from the clinical routine of school doctoring, his interest in all things medical was as lively as ever. He sat on committees—one of them being the Medical Officers of Public Schools Subcommittee of the B.M.A.—and in debate made gently expressed but extremely sane contributions. He was indefatigable in attending medical meetings right up to the time of his death, and was ready to add some well-informed remarks to discussions on almost any medical topic. Before retirement he held office for a time as president of the Medical Officers of Schools Association.

For some boys he stood in a rather special position, since in his early days at Wellington he combined the job of school doctor with that of housemaster in charge of a waiting house. Many generations of Wellingtonians will remember him with affection.

H. R. TIGHE, M.D., F.R.C.S.I., D.P.H.

Dr. H. R. Tighe, a former medical officer of health and school medical officer of Swansea, died suddenly at Morriston Hospital on June 20, after a short illness. He retired in June, 1949, having been in office since 1939, after serving as deputy to the late Dr. Thomas Evans from 1920.

Harman Richard Tighe was a native of Southern Ireland and qualified in 1910, obtaining the F.R.C.S.I. in the following year. In 1914 he took the D.P.H. at Liverpool and held his first public health post as assistant school medical officer in that city. In 1920 he came to Swansea, and 12 years later he took the degree of M.D. at the University of Durham. A man of distinction and of the highest integrity, during the whole of his time in Swansea he was looked upon as an authority on preventive medicine, which he did much to promote. He took an active part in the medical life of Swansea, serving for some years as honorary secretary of the Swansea Division of the B.M.A., and being chairman of the Division from 1936 to 1937. He had also been president of the Welsh Branch of the Society of Medical Officers of Health. Those who served under Dr. Tighe have the happiest memories of his charm and kind personality and mourn his passing. He is survived by his wife, his son, Dr. J. R. Tighe, and two daughters, one of whom is medically qualified.

B. W. ARMSTRONG, O.B.E., *M.C.*, M.B.

The obituary of Dr. B. W. Armstrong was printed in the *Journal* of June 14 (p. 1422).

Dr. P. SZUMOWSKI writes: For 31 years the Royal Sea Bathing Hospital had been Dr. Armstrong's home, his work, his life. Even after his retirement from the post of medical superintendent in 1954 he never completely lost contact with the hospital, continuing to serve as honorary consultant surgeon and president of the League of Friends of the hospital. He told me he was always extremely happy here. Although I knew him only for a short time, I formed the impression that his medical work was for him not merely a profession—it was something much more. He lived for his work and for his personal contact with the sick. He was first of all a friend of his patients. He lived with them through their sufferings, great and small, and he found with them the way to a happy recovery. They always remained his personal friends. No wonder I have seen a patient coming to "her Dr. Armstrong" for routine check-up all the way from New Zealand. Apart from his being one of the leading authorities in his specialty, surgical tuberculosis, Dr. Armstrong had always been a pioneer and artisan in his work. For him his work was an art and a constructive one. He was a perfectionist in everything he said or did, be it something big and important or some small and seemingly unimportant detail, and this art he taught to his staff and in fact to everybody working in the hospital. Under Dr. Armstrong there prevailed in the hospital the spirit of professional pride and perfection. I am sure that many technical achievements of the highest standard in the treatment and nursing of long-standing surgical tuberculosis illnesses in the Royal Sea Bathing Hospital were entirely due to his inspiration and scrupulous work. The plaster and splint departments are second to none in the country. He certainly made the Royal Sea Bathing Hospital what it has been during the last three decades—well known in this country and abroad. He knew where and how to find the "proper people" for the proper place in the hospital, and during this time he succeeded in forming a team of most devoted and inspired workers in all departments. It was his personality which was the secret of his success and achievement. He was full of charm, deep culture, with wide cosmopolitan interests, and with special consideration for everyone, thereby enabling him to be respected and admired by his staff and his patients. He was the last medical superintendent of the Royal Sea Bathing Hospital, and with his retirement closed a chapter in its history. It was a pity that he had so little time after his retirement, and his activities were further curtailed by a progressively debilitating disease.

Lord WEBB-JOHNSON, G.C.V.O., C.B.E., D.S.O.
Hon.LL.D., M.B., Ch.B., F.R.C.S.

The memorial service for Lord Webb-Johnson was held at St. Margaret's, Westminster, on June 26. The church was filled by a very large gathering of relatives, private and professional friends, and representatives of the many institutions with which Lord Webb-Johnson was connected. The Queen was represented by Lord Evans. The Rev. C. L. Creswell and Canon Michael Stancliffe conducted the service, and Sir Gordon Gordon-Taylor read a passage from *Proverbs* beginning: "Happy is the man that findeth wisdom, and the man that getteth understanding."

Medico-Legal

AN UNEXPECTED BABY

[FROM AN OBSTETRIC CORRESPONDENT]

On March 17 the Birmingham Coroner's Court investigated an unusual neonatal death (*The Times*, March 18). The mother of the baby said that she did not realize she was pregnant and in labour until after the waters broke. Four years previously she had had a normal pregnancy and labour. In her evidence she stated that she had spent a year in the Far East with her husband prior to sailing for England on May 12, 1957. While abroad she discovered that her husband wanted to marry someone else, but she had shared a bedroom with him shortly before her departure for England. She had no idea that she was pregnant, because she had no symptoms. Her periods had continued regularly and she had felt no movements. On getting up on February 27, 1958 (i.e., 291 days after embarkation), she had started to have some vaginal bleeding which she took for the start of her normal period. Later in the morning she had very severe pain, but still did not realize what was happening and sat on the toilet, where the waters broke. The baby had been born very suddenly while her mother, to whom she had called out, was getting help. She stated, "If I'd realized I was pregnant, I'd have seen my doctor and have prepared for the child—even if I had divorced my husband I'd still have wanted it." The woman's mother, mother-in-law, and next-door neighbour all affirmed that they had not suspected that she was pregnant.

The pathologist who carried out a necropsy on the baby the day after its birth said that the child had been born alive and had breathed. No water was found in the air passages. In his opinion the death of the baby, which weighed 6 lb. 15 oz. (3.3 kg.), was due to shock from immersion in water. He stated that he had known of about half a dozen cases where the mother had not known she was pregnant, including a woman who had previously had 10 children.

The coroner recorded a verdict of death from lack of care and attention at birth.

Comment

One of the most interesting features of this case was the affirmation by a parous woman that she did not know she was pregnant until the baby was actually being born. Most obstetricians of experience have encountered cases where a woman found to be advanced in pregnancy, or even in labour, denies awareness of being pregnant, and sometimes, as in the case cited, there is no history of amenorrhoea. Usually, however, the patient is primigravid and unmarried, and it is tempting therefore to draw an analogy between these cases and those of pseudocyesis. Fried *et al.*[1] remarked that spurious pregnancy commonly followed a situational stress which would best be resolved by the presence of pregnancy. The patient's basic mental conflict made it desirable that she should be pregnant, and therefore she developed all the symptoms and some of the signs of pregnancy, even to the point of her doctor being deceived. Presumably, by a similar mechanism, the symptoms of a true pregnancy might be suppressed or denied conscious recognition because the pregnancy was not in the particular circumstances welcome. But if this can happen it is surprising that pregnancy unsuspected by the mother is not encountered more often.

REFERENCE

1 Fried, P. H., Rakoff, A. E., Schophach, R. R., and Kaplan, A. J., *J. Amer. med. Ass.*, 1951, **145**, 1329.

DROWNED IN NINE INCHES OF WATER

[FROM AN EXPERT IN FORENSIC MEDICINE]

At 2 p.m. on February 1 a boy of nearly 13 finished his midday meal and went out to play. A quarter of an hour later he was found lying face down in a brook in the playing fields behind his home in Sutton Coldfield. The water was nowhere more than 9 in. (23 cm.) deep, and indeed did not cover his head. Artificial respiration was carried out without response until 2.50 p.m., when a doctor arrived and pronounced the boy dead. Post-mortem examination showed no marks of violence, no congenital defects, and no organic disease. The stomach contained a large undigested meal. Petechial haemorrhages were noted upon the heart and lungs—a rather unusual finding in death from drowning—but gravel as well as froth was found in the ballooned lungs, leaving little doubt that the immediate cause of death was, in fact, drowning. A police sergeant is reported to have said that a cigarette was found on the bank of the brook, and that the boy had a packet of the same brand in his pocket.

Another recent fatality from drowning occurred in a pool on Tooting Bec Common. On April 11 at 12.39 p.m. a small boy ran up to the Common keeper and told him that another small boy had fallen into a pool. The keeper ran to the pool and saw the body of a child of 2½ lying on the bottom in 3 to 4 ft. (about 1 metre) of water. The body was recovered, immediate first-aid given, and an ambulance summoned. The boy reached the casualty department of St. James's Hospital at 12.55 p.m. Here further resuscitative measures were instituted, including cardiac massage, and at 1.25 p.m. the heart began to beat. Spontaneous respirations returned and the child made remarkable progress until at 9 p.m. that evening what were thought to be purposive movements were observed. A tracheotomy was performed but the child died about 20 minutes later. Post-mortem examination showed partial collapse of the lungs with a great excess of mucus throughout the air passages.

Comment

Theories on the mechanism of death in drowning have been rationalized in the last few years. The work of Swann and Brucer[1 2] suggests that the interval between immersion and cardiac arrest is almost 3½ minutes in fresh water and 10 minutes in sea water; and, further, that the cause of death in fresh-water drowning is haemodilution and overloading of the heart, while in salt-water drowning fluid is sucked by osmosis from the circulation into the lungs so that acute pulmonary oedema develops.

The two cases noted here present a strange contrast: the elder boy falls into a shallow stream in conditions of apparently minimal danger, while the small boy falls into a pool where every circumstance would seem to be against him—and yet is kept alive for six hours. This contrast makes one wonder whether there was not some extraneous circumstance in the case of the elder boy, one which would not be obvious to the pathologist. Among such could be epilepsy, some form of vagal shock followed by drowning, or the very remote possibility that he had been held under water. There was of course speculation at the inquest and in the press as to why this healthy boy should have drowned in such shallow water, especially as he had ready access to the brook and had often played around and in it. Epilepsy might be an explanation, though there was no history of fits. Nor was there anything in the post-mortem findings to suggest epilepsy—e.g., a bitten tongue or empty bladder—though these findings would not necessarily be present after a fit. A cigarette was picked up near the boy, and smoking one at that early age could undoubtedly cause giddiness and might result in a fall into the brook. But one would have thought that giddiness from smoking or an ordinary faint would have been as effectively relieved by falling into water as by most stimulants.

At the inquest on the younger boy doubts were expressed whether after such a prolonged period of anoxia full cerebral recovery could have been expected. However, the partial recovery in this case does underline the value of modern resuscitative measures, including cardiac massage, in cases of drowning and electrocution.

REFERENCES

1 Swann, H. G., and Brucer, M., *Tex. Rep. Biol. Med.*, 1949, **7**, 604.
2 —— —— Moore, C., and Vezien, B. L., *ibid.*, 1947, **5**, 423.

Medical Notes in Parliament

ANSWERS TO QUESTIONS

Student Grants

Mr. G. LONGDEN (South-west Hertfordshire, Con.) asked the Minister of Education on June 25 whether he would make a further statement about the arrangements for financial awards to university students. Mr. GEOFFREY LLOYD said that with the Secretary of State for Scotland he had decided to set up a committee with the following terms of reference:

"To consider the present system of awards from public funds to students attending first degree courses at universities and comparable courses at other institutions and to make recommendations."

The committee would therefore consider the kinds of awards to be made from public funds, the method of selecting students for such awards, and the principle of the hardship test required by the law as it now stands. Sir Colin Anderson had accepted the Government's invitation to act as chairman, and the other members of the committee were: Mrs. Gladys Buxton (chairman, Derbyshire County Council), Mrs. Margaret Cooke (Birmingham City councillor), Mr.

W. McL. Dewar (headmaster, George Heriot's, Edinburgh), Miss J. A. Evans (headmistress, Keighley Girls' Grammar School), Mr. W. W. Finlay (governor, Scottish College of Commerce, Glasgow), Mr. Norman Fisher (principal, Staff College of the National Coal Board), Alderman J. W. E. Hill, Kt. (president of council, Nottingham University), Mr. H. D. P. Lee (headmaster, Winchester College), Dr. D. W. Logan (principal, London University), Mr. Ron Smith (secretary, Union of Post Office Workers), Dr. L. S. Sutherland (principal, Lady Margaret Hall, Oxford), Professor Brinley Thomas (professor of economics, University College, Cardiff), Dr. J. Topping (principal, Brunel College of Technology, Acton), Mr. A. H. Wilson (managing director in charge of research and development, Courtauld's Ltd.), and Professor E. M. Wright (professor of mathematics, Aberdeen University). The secretaries of the committee were Mr. D. Neylan (Ministry of Education) and Mr. G. A. T. Hanks (Scottish Education Department).

Tests for Radioactive Fall-out

Mr. TUDOR WATKINS (Brecon and Radnor, Lab.) asked the Prime Minister on June 25 whether, in view of the strong representations from Wales about the periodic tests for radioactive fall-out, he would give instructions that reports were to be written in a non-technical form, easily understandable to the public; and whether, to reassure the population in the upland areas, he would publish in simple non-technical terms the incidence of fall-out and the level of strontium-90 in these areas, and give in non-scientific terms information that would help lay persons in assessing the danger from fall-out. Mr. MACMILLAN replied that the Government were considering whether they could improve the presentation of the results of measurement of fall-out. He pointed out, however, that the assessment of the significance of these results was a complicated and technical matter. The forthcoming report of the United Nations Scientific Committee on the effects of atomic radiation would, he understood, contain an up-to-date assessment of the health hazards due to radiation.

Mr. WATKINS, and some others, pressed the point that people were getting alarmed and wanted to know in simple language what it really meant to them and whether they could carry on earning their livelihood at sheep farming. Mr. MACMILLAN replied that, in simple language, he was advised that the levels did not constitute any danger to the human population, but there was always rather a difficulty in trying to express these highly technical results in too simple a form.

Duty on Drugs

Mr. J. SNOW (Lichfield and Tamworth, Lab.) asked the President of the Board of Trade if he would re-examine, under the terms of the Safeguarding of Industry Act, 1921, and subsequent amending legislation, the key industry duty payable on steroid hormones and certain antibiotics and vitamins, in order to satisfy himself that prices charged to the Health Service in respect of certain drugs were reasonable, and were made controllable by varying such key industry duties in the light of recent pharmaceutical discoveries and productions in the United Kingdom and elsewhere.

Sir DAVID ECCLES replied that prices of drugs under the Health Service were a matter for the Minister of Health. If an application by users for a change in the duty on any of these drugs were made to him, he would consider whether any action was called for.

Mr. SNOW explained that his question had been "a ranging shot" to draw attention to the fact that the powers under this Act might be a small way to control the high cost of some drugs. Sir DAVID ECCLES reminded him that the key industry duty would lapse at the end of this year and would be embodied in the new tariff schedule, in which case changes could be made more simply.

Research and Propaganda on Lung Cancer

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked on June 30 what contribution, financial or otherwise, was being made by the Ministry of Health in relation to research and propaganda on the connexion between cancer of the lung and smoking. Mr. R. THOMPSON, Parliamentary Secretary, stated that cancer research at public expense was being undertaken by the Medical Research Council and within the Health Service, but it was not possible to say how much was spent on research into smoking and lung cancer. Copies of a report by the Council and of a statement made in the House on June 27 last year were sent to local health authorities with the request that they should publish in their campaigns on health education information about the risks of smoking. These campaigns attracted 50% Exchequer grant. He added that the Minister would shortly be asking local authorities for reports on the action they had taken.

Transistor Hearing-aids

The MINISTER OF HEALTH informed Mr. EDWARD EVANS (Lowestoft, Lab.) that the full-scale clinical trials of the Medresco transistor aid held last year with 400 patients showed that the aid was generally satisfactory but that the microphone should be improved and clothes rub reduced. These, together with a number of other minor improvements, were made and the production samples were found to be acceptable. Production had now started.

PROFESSIONAL SUBSCRIPTIONS

The relief given in the Budget for subscriptions to professional and learned societies as deductible expenses for income-tax purposes was further discussed during the committee stage of the Finance Bill on June 17. Mr. ERIC FLETCHER (Islington, East, Lab.) moved an amendment to Clause 14 to extend the concession to local societies. A great many of these learned societies, he said, were "of a mainly local character"—which the clause excluded—and they were just as deserving of support as national organizations. Mr. G. STEVENS (Portsmouth, Langstone, Con.), supporting the amendment, said that a good deal of the work of advancement and spread of knowledge and the maintenance or improvement of standards of conduct was devolved upon local district societies, which played an extremely important part. Mr. J. CRONIN (Loughborough, Lab.) reinforced the argument with the illustration of a doctor's relationship to the Royal Society of Medicine, which was a national body, and the Chelsea Clinical Society, an equally useful body, that was completely ruled out.

Administrative Difficulty

Mr. J. E. S. SIMON, Financial Secretary to the Treasury, agreed that there was no logical reason why local societies should be excluded. Just as good a case could be made for them, until the administrative difficulty of including them was considered. Generally speaking, there was a strong social and recreational element in the local societies; the luncheon-club element was quite strong. Scientific and social elements were inextricably mixed. Every one of the local societies would have to be examined by the Inland Revenue to see whether its activities qualified. It was reckoned that the national societies would probably number about 3,000. Even that was putting a considerable burden on the Inland Revenue. To add all the local societies would mean that the administration would break down. Generally speaking, the subscriptions to local societies were quite small, and, whatever the logic, there was no real grievance or hardship. The amendment was withdrawn after further discussion.

HOUSE OF LORDS

Cruelty in Divorce Petitions

The Divorce (Insanity and Desertion) Bill has gone through the Lords unchanged in respect of cruelty attributable to mental causes. On the report stage on June 26 Lord SILKIN renewed the attempt to insert a new clause providing that it should be no defence against a petition that the person responsible for the cruelty was suffering from disease of the mind at the time—a contention for

For treatment of **all** severe, recurrent

or chronic

URINARY INFECTIONS

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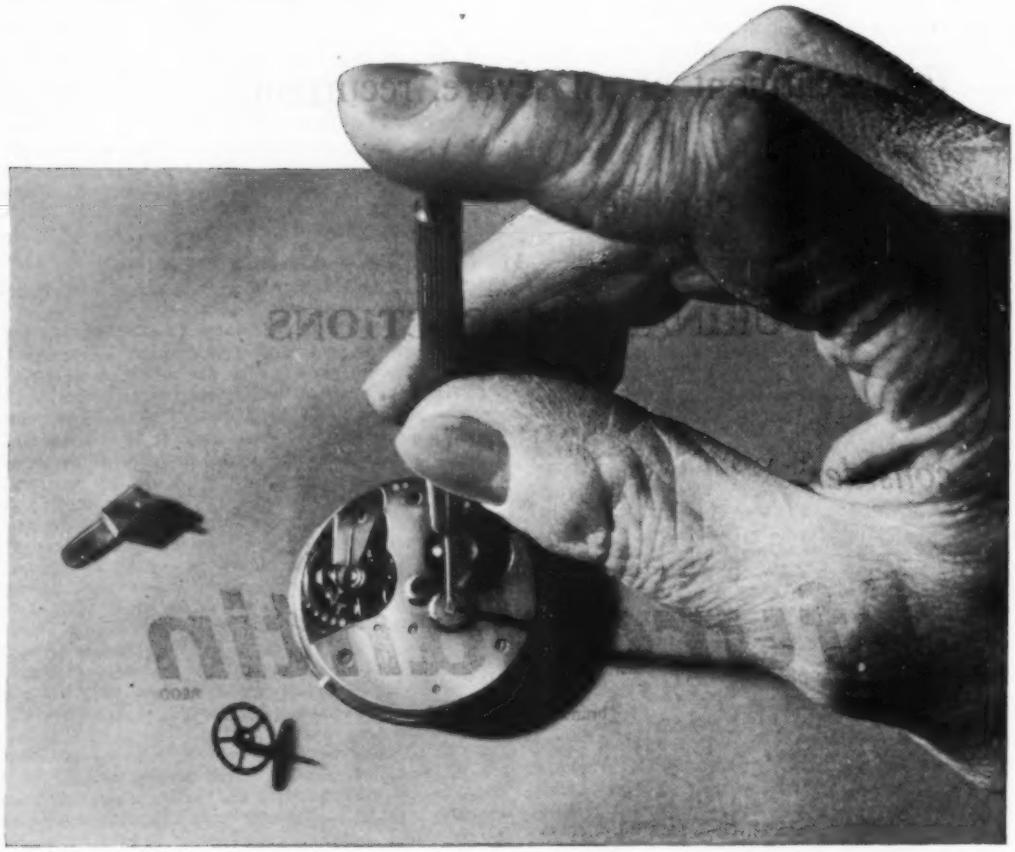
This man has Parkinsonism



but he also has

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The classic treatment for postencephalitic, arterioscleratic and idiopathic Parkinsonism

ELIXIR *2 mg. per 5 cc. Bottles of 16 fl. oz.*

TABLETS *2 mg. and 5 mg. Bottles of 100 and 1,000*

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which he claimed unanimous support by the Royal Commission on Marriage and Divorce. The LORD CHANCELLOR pointed to the conflict of hardship that arose. If the amendment were accepted it would mean that a husband would be branded with cruelty when, at the time the alleged cruelty was committed, he did not know what he was doing, or that what he was doing was wrong. On the other hand there was hardship to the wife if she was unable to get a divorce without having to wait a period of years until it was determined that the insanity was of a permanent kind. Among those he had consulted, he said, strong views were held either way. In the circumstances, he urged Lord Silkin not to pursue the amendment. The Bill did much useful work outside the field of controversy, and it would be unfortunate to jeopardize that advantage. The amendment was withdrawn, and the report stage concluded.

Opticians Bill

The Opticians Bill was given its third reading in the House of Lords on June 24.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on June 7 the following degrees were conferred:

D.M.—J. Towers.
B.M.—*In absence:* P. F. B. Owen.

UNIVERSITY OF CAMBRIDGE

In Congregation on June 7 the following degrees were conferred:

M.A.—Diana M. Brinkley, M.B., B.S., D.M.R.T.
M.D.—A. McGregor, K. E. K. Rowson, F. D. Schofield, C. C. D. Shute.
M.B., B.CHIR.—*By proxy:* T. H. Almond.
M.B.—D. Freeman (*by proxy*), R. B. Cole, A. E. Holmes.
M.B., B.CHIR.—D. Freeman (*by proxy*), R. B. Cole, A. E. Holmes.

The following candidates have been approved at the examinations indicated:

FINAL M.B.—*Part II:* [1 2 3]A. R. Adamson, [2 3]A. J. R. Anderson, [1 2]E. C. Ashby, [1 2 3]D. I. Atkinson, [1 2]C. I. Backhouse, [1 2 3]J. S. Bailey, [1 2 3]P. J. Ball, [1 2 3]J. E. Banatvala, [1 2 3]M. Barry, [1 2 3]J. R. Bartlett, [1 2 3]A. C. Bayley, [1 2 3]P. J. Beale, [1 2 3]D. L. Belcher, [1 2 3]P. M. J. Bennett, [1]G. A. Bewley, [1 2 3]D. A. Birkett, [1 2]R. B. B. Bishton, [1 2 3]J. Blake, [1 2 3]S. S. Bleehen, [1 2 3]S. A. Bolt, [1 2 3]P. D. G. Briggs, [1 2 3]G. C. Brill, [1 2 3]M. H. Brooke, [1 2]J.-P. C. M. Brookes, [1 2 3]E. P. Brooks, [1 2 3]F. T. Brough, [1 2 3]J. M. Brown, [2]I. F. M. Buchanan, [1 2 3]M. U. Bullen, [2]H. P. R. Bury, [1 2 3]W. D. Callum, [1 2]A. J. P. Campbell, [1 2 3]I. G. Carnegie Brown, [1 2 3]C. J. Carr, [1 2 3]I. R. Carr, [1 2 3]I. Chippendale, [1 2]I. G. Christie, [1 2 3]P. W. Clements, [1 2]G. F. Cohen, [1 2 3]R. D. Cohen, [1 2]M. Colebrook, [1 2 3]M. J. Corrigan, [2]D. D. Craig, [1]J. Craske, [1 2 3]A. D. Crawford, [1]P. A. Cullum, [1 2 3]J. R. B. Currie, [1 2 3]D. Davies, [1 2 3]G. M. Davies, [1 2 3]M. H. Davies, [1 2 3]N. Davies, [1 2 3]D. D. Devine, [1 2]H. F. Don, [2]C. E. Durrant, [1 2 3]A. J. Earl, [1 2 3]R. J. Earlam, [1 2 3]J. S. Elkington, [1 2]C. B. d'A. Fearn, [1 2 3]R. C. L. Feneley, [1 2]M. Fisher, [1 2]P. J. Folca, [1 2 3]R. M. M. Fordham, [1]W. E. I. Forsythe-Jauch, [1 2 3]P. B. Garland, [1 2 3]T. W. Gibson, [2]J. E. Godrich, [1 2 3]R. J. M. Gold, [1 2]P. H. T. Greig, [1 2]J. S. Grimshaw, [1 2 3]R. B. Harcourt, [1 2 3]J. D. Hardcastle, [2]N. A. Harker, [1 2 3]D. C. Harvey, [1 2 3]W. R. Heaton, [1 2 3]J. Hedley-Whyte, [1]R. S. Hickling, [1 2 3]A. A. Hooper, [2]A. L. Hovenden, [1 2 3]J. R. Hoyle, [1 2 3]Y. P. Humphreys, [1 2]P. V. Hunt, [1 2 3]I. D. Hunter-Craig, [2]T. A. Hussell, [2]R. K. Jackson, [2 3]P. B. Jacobs, [2]S. A. Janmohamed, [1]A. B. C. Jefferson, [1 2 3]J. D. Jeremiah, [1 2 3]M. L. Johnson, [1 2 3]R. H. Johnson, [1 2]I. N. L. Johnston, [1 2 3]A. E. Kermode, [1 2 3]R. A. Kipping, [1 2 3]C. G. Koo, [1 2]L. Kwasny, [2]J. G. Lancaster, [2]M. I. Lander, [1 2]A. M. D. Langford, [1 2 3]J. R. Langmaid, [1]R. D. B. Leicester, [1 2 3]N. K. Leiper, [1 2 3]P. O. Liebling, [1 2 3]R. M. Lodge, [1 2]D. B. MacAdam, [1 2]I. D. McIntosh, [1 2 3]J. W. Mack, [1 2]J. G. McLaggan, [2 3]J. S. Macve, [2]C. McL. Maddox, [1 2]T. S. Matthews, [1 2 3]R. J. Mitchell, [1 2]T. M. Mitchell-Fox, [1 2 3]T. Moreton, [1 2 3]H. G. Morgan, [1 2 3]M. G. E. Morgan, [1 2]I. S. Muir, [1 2 3]B. Newbigin, [1 2 3]N. W. Oakley, [1 2 3]M. J. O'Shea, [1 2 3]J. D. Owen, [1 2 3]J. S. Paddle, [2 3]J. D. J. Parker, [1 2 3]P. W. S. Patton, [1 2 3]E. N. Payne, [2 3]D. H. Perkins, [1 2 3]P. V. Pigott, [1 2]J. N. Powell, [1 2 3]M. L. B. Pritchard, [1 2 3]G. E. T. Raine, [1 2 3]M. J. Ramsden, [1 2 3]M. J. Raphael, [1 2 3]R. J. Read, [1 2]M. M. R. Reid, [1 2 3]A. Reynolds, [1 2]D. Rhys-Phillips, [1 2 3]J. C. Rice, [1 2 3]A. B. Richards, [1 2 3]B. Richards, [1 2 3]D. J. Richards, [1 2]G. K. Richards, [1 2]R. M. Ridsdill-Smith, [2]G. A. Robson, [1 2]N. C. Roles, [2]V. Rudralingam, [1 2 3]H. M. Rumsey, [1 2 3]N. Sankarayya, [1 2 3]D. C. L. Savage, [1 2 3]W. G. Shakespeare, [1 2 3]J. M. Shepherd, [1 2 3]R. W. Sherwin, [2 3]R. M. Simons, [1 2 3]M. R. Skelton, [1 2 3]A. C. Smith, [1]I. S. Smith, [1 2 3]T. A. L. Smith, [1 2 3]J. W. Soper, [1 2 3]J. C. Southam, [2]S. Sprague, [1 2 3]J. E. Stark, [1 2 3]J. M. Stephenson, [2 3]D. J. D. Stevenson, [1 2]J. D. M. Stewart, [1 2]J. R. Strong, [1 2 3]S. O. Suite, [1 2 3]G. C. Sutton, [1 2]P. H. Tatham, [1 2 3]R. E. Tattersall, [1 2 3]A. J. Taylor, [1]J. S. H. Tooth, [1 2 3]M. E. Tuck, [1 2 3]H. B. Valman, [1 2 3]M. Walker, [1 2 3]D. M. Ward, [1 2]J. B. Warren, [1 2 3]D. B. Watkin, [2]J. Weston, [1 2 3]W. F. Whimster, [1 2 3]D. M. Whiteford, [1 2 3]A. Whitworth, [1 2 3]D. H. Whyte-Venables, [1 2]R. P. Wilding, [1 2 3]M. E. Wilson, [2]F. G. de L. Wright, [1 2 3]R. Yeo. *Part I (Pathology and Pharmacology):* P. J. Ball, M. D. Begley, P. M. J. Bennett, F. T. Brough, M. H. Bull, F. M. Cameron, A. J. P. Campbell, I. R. Carr, I. G. Christie, H. S. Cormack, D. D. Craig, I. R. B. Currie, N. Davies, T. T. Davies, C. B. d'A. Fearn, W. E. I. Forsythe-Jauch, A. L. Hovenden, A. Kenyon, A. M. D. Langford, D. B. MacAdam, I. D. McIntosh, J. W. Mack, K. I. Mackenzie, C. McL. Maddox, J. M. Maitland, P. W. S. Patton, P. V. Pigott, R. J. Read, D. Rhys-Phillips, A. B. Richards, R. M. Ridsdill-Smith, R. M. Simons, J. R. Strong, P. H. Tatham, A. J. Taylor, S. D. Turner, J. E. C. Twentyman, S. O. Wamuo.

Dr. E. H. R. Ford, University Demonstrator in Anatomy, has been elected to a Fellowship and College Lectureship in Anatomy of Selwyn College.

[1]Passed in principles and practice of physic. [2]Passed in principles and practice of surgery. [3]Passed in midwifery and gynaecology.

UNIVERSITY OF LONDON

The degree of M.D. was awarded by the Senate to E. J. Ross on May 21.

UNIVERSITY OF WALES

The following candidates at the Welsh National School of Medicine have been approved at the examination indicated:

M.B., B.CH.—[1]T. J. Bayley, D. Bevan, B. Davies, R. J. Davies, J. G. Edwards, D. R. Evans, J. D. Evans, R. R. Evans, D. R. Freebury, J. B. T. Griffiths, Madeline F. M. Gunn, Jean Hellings, R. L. H. Hughes, J. E. A. Kenrick, [2 3]W. C. Lane, Reza Larizadeh, D. W. Lewis, Rena Lewis, A. R. Lloyd, [2 4]M. P. Mahoney, P. J. McCarthy, Mary H. Morgan, R. B. Morgan, C. H. Naylor, T. Powell, D. J. Sadler, C. S. Selby, J. A. Wyatt, Tada Yipintsoi.

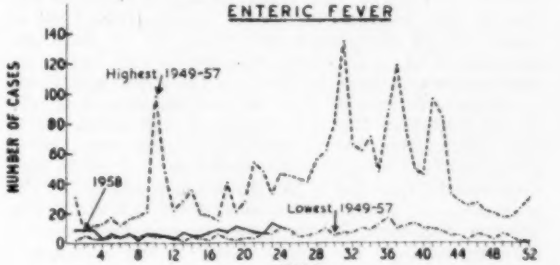
TUBERCULOUS DISEASES DIPLOMA.—Don V. P. Abayagunawardana, G. F. Abdul Rahim, C. Brahma, W. Chan, C. D. Chelliah, S. De, S. Devi, Wen-Chu Huang, V. K. Jayaram, J. A. Mahoney, S. K. Mukhopadhyay, B. K. Patnaik, Philine T. Pieris, S. K. Ray, J. N. Razdan, J. Sacco, H. Singh.

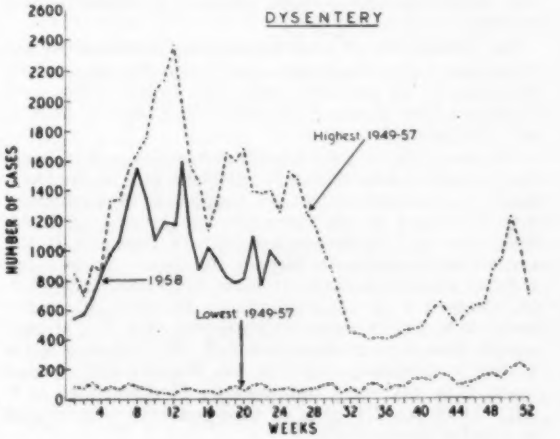
[1]With distinction in surgery. [2]With distinction in human anatomy. [3]With distinction in pathology and bacteriology. [4]With distinction in social medicine and public health.

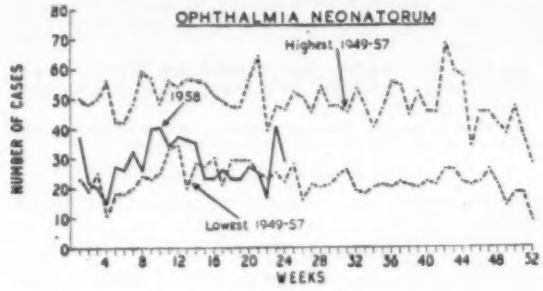
Vital Statistics

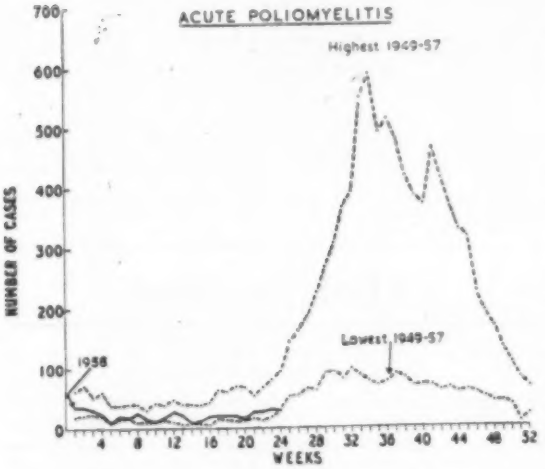
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending June 21

The largest fluctuations in the notifications of infectious diseases in England and Wales during the week ending June 21 were increases of 514 for measles, from 5,594 to 6,108; 53 for whooping-cough, from 747 to 800; and decreases of 53 for dysentery, from 891 to 838; and 33 for acute pneumonia, from 247 to 214. The largest rises in the notifications of measles were 165 in Lancashire, from 672 to 837 (Liverpool C.B. 237, Blackburn C.B. 214); 112 in Devonshire, from 144 to 256 (Exeter C.B. 129); 84 in Somersetshire, from 121 to 205 (Bath C.B. 145); 66 in Nottinghamshire, from 219 to 285 (Nottingham C.B. 145). The notifications of scarlet fever numbered 657, 9 fewer than in the preceding week, and there were no large fluctuations in the local returns. The largest increase in the incidence of whooping-cough was 20 in Somersetshire, from 8 to 28. For the second consecutive week no case of diphtheria was notified.

The notifications of acute poliomyelitis numbered 36, and these were 2 more for paralytic and 5 more for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 9 (Halifax C.B. 3, Morley M.B. 2) and Lancashire 5.

The areas returning the largest number of cases of dysentery were Yorkshire West Riding 195 (Barnsley C.B. 42, Huddersfield C.B. 27, Sheffield C.B. 26, Leeds C.B. 13, Rotherham C.B. 12, York C.B. 12), Lancashire 154 (Liverpool C.B. 48, Manchester C.B. 16, Rawtenstall M.B. 14, Oldham C.B. 10), London 60 (Islington 11, Stepney 10), Surrey 58 (Banstead U.D. 42, Carshalton U.D. 11), Essex 50 (Walthamstow M.B. 27, Chigwell U.D. 17), Staffordshire 39 (Newcastle-under-Lyme M.B. 25), Durham 35 (Hartlepool M.B. 17), Middlesex 33, Hampshire 26 (Droxford R.D. 17), Yorkshire North Riding 26 (Middlesbrough C.B. 24), Warwickshire 25 (Bedworth U.D. 14), and Cambridgeshire 25 (Cambridge M.B. 25). 75 of the 279 cases of food-poisoning were notified in London (Stepney 57).

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **June 14** (No. 24) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	0	0	1	0		8	2	3	0	2
Dysentery	891	65	184	15	4	457	38	194	6	1
Encephalitis, acute	4	0		0		5	1		0	
Enteric fever:										
Typhoid ..	8	0	0	0		7	1	0	0	
Paratyphoid ..	2	0	3(B)	0	5(B)	3	1	2(B)	0	
Food-poisoning ..	275	14	351	0		125	25	19	0	
Infective enteritis or diarrhoea under 2 years				14	24				14	15
Measles *	5,594	457	133	34	53	21,793	856	214	250	154
Meningococcal infection	15	5	9	2	2	15	1	11	0	
Ophthalmia neonatorum	29	4	1	0		36	3	3	0	
Pneumonia † ..	247	19	112	3	1	308	27	118	3	2
Poliomyelitis, acute:										
Paralytic ..	20	2	6	3	4	41	6	2	7	4
Non-paralytic ..	9	0				42	3			
Puerperal fever: § ..	200	22	10	0		185	38	4	0	
Scarlet fever ..	666	48	70	14	31	547	32	78	24	14
Tuberculosis:										
Respiratory ..	558	59	111	18		469	51	178	19	
Non-respiratory	108	10	14	5		22	1	18	3	
Whooping-cough ..	747	37	91	10	30	1,371	39	152	6	49

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	1	0	0		0	1	0	0
Influenza	9	0	0	0	1		0	1	0	0
Measles		1	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	328	16	17	6	8		32	12	8	5
Poliomyelitis, acute	1	0		0	0		0			0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	81	5	2	0	5		2	3	0	5
Non-respiratory		1	2	0	0		1	3	0	1
Whooping-cough ..	0	0	0	0	0		0	0	0	0
Deaths 0–1 year ..	315	36	26	8	10		17	30	5	14
Deaths (excluding stillbirths) ..	8,639	682	523	110	157		592	559	104	138
LIVE BIRTHS ..	14,662	1294	971	210	436		1105	993	247	454
STILLBIRTHS ..	324	20	25				26	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

N.A.P.T. Commonwealth Chest Conference.—The Commonwealth Conference, which incorporates the British Tuberculosis Association's annual conference, opened in London on July 1. The DUCHESS OF KENT, president of the National Association for the Prevention of Tuberculosis, performed the opening ceremony. Besides problems concerned directly with tuberculosis, the Conference's wider interests are shown by the inclusion in its programme of discussions on leprosy and tuberculosis, environmental factors in respiratory disease, the management of the heart in chronic respiratory disease, and the problem of lung cancer. After the four days of scientific sessions, there were tours and visits for the delegates.

Poliomyelitis Centre.—On June 25 the EARL OF LIMERICK, chairman of the Medical Research Council, opened a poliomyelitis research centre at Hendon Isolation Hospital, London, N.W.9. The centre is under the direction of Dr. A. B. KINNIER WILSON, and the Institute of Orthopaedics (London University) will administer it. Dr. Kinnier Wilson is specially interested in artificial respirators and rehabilitation. The centre is the outcome of a recommendation in 1951 by a committee of the Royal College of Physicians of London for a unit to carry out research on the clinical aspects of poliomyelitis, and the proximity of the centre to the Public Health Laboratory Service's virus reference laboratory at Colindale will be useful in investigations of other viral diseases of the central nervous system. The Royal National Orthopaedic Hospital, Stanmore, is assisting in staffing the unit.

Ciba Foundation.—The names of the nine winners of the Foundation's 1958 awards for research relevant to the problems of ageing have now been announced. The two winners of £300 prizes are Dr. R. J. BOUCEK, of Miami, and Dr. D. S. MCLAREN, of Mwanza, Tanganyika, the latter for a report entitled "Age and Nutrition in the Aetiology of Cataract." Dr. A. COMFORT (University College, London) is one of the four winners of £200. These awards are being offered for the last time next year, the closing date being January 10, 1959. The Ciba Foundation issued its annual report for 1957 recently. During that year over 800 scientific visitors from 35 countries were provided with rooms. Among its other activities the Foundation held six international conferences, and, as a new venture, five study groups. The conferences were on hormones in the blood, the mechanisms of drug resistance, the mucopolysaccharides, the C.S.F., hormone-producing tumours, and the neurological basis of behaviour. The Foundation's address is 41, Portland Place, London, W.1.

Speeding Medical News.—The Institute for Advancement of Medical Communication, New York, announces its establishment as a non-profit organization to study and develop ways of facilitating the exchange of information between medical scientists, medical educators, and practising physicians. The Institute intends to do this by devising and testing methods of disseminating medical information which promise advantages over those in present use and by serving as an information centre for medical organizations wanting help with communication problems. The Institute will be financed by general and research grants from private foundations and from agencies, private and Federal, which support medical research. The charter members of the Institute's board are Professor CHAUNCEY D. LEAKE, Ph.D., professor of pharmacology, Ohio State University; Professor HOMER W. SMITH, professor of physiology, New York University; Professor IRVING S. WRIGHT, professor of clinical medicine, Cornell University. Dr. RICHARD H. ORR, assistant editor of *Metabolism* and formerly medical director of Messrs. Grune and Stratton, Inc., is executive director, from whom further details may be obtained at the Institute's temporary headquarters, 37, East 67th Street, New York, 21.

F.R.C.S.—The following were successful in the recent examination for the Fellowship of the Royal College of Surgeons of England:

G. B. Northcroft, V. M. Thompson, W. B. Ashby, R. S. Sneath, F. R. Coffin, A. E. Buckle, P. L. C. Diggory, A. Gillespie, F. J. Moynihan, J. M. Powley, W. J. Pryn, D. M. Millar, K. R. S. Pool, R. Y. Calne, A. R. Bearn, R. James, P. S. Boulter, G. Hayes, J. Mutch, I. K. Mikhail, A. K. Chowdhury, W. Lees, K. A. McCluskey, K. A. Menon, J. Y. Fowler-Wright, H. Harrop-Griffiths, N. H. Harris, R. H. Lewis, A. H. Petty, K. Bloor, H. C. Brown, T. I. El-Gailani, J. Magri, G. A. W. Milner (Otolaryngology), R. F. Rohan (Otolaryngology), D. S. Sardana (Otolaryngology), C. B. Walker (Ophthalmology), K. R. Alimchandani, D. S. Dharmage, J. L. A. Dowse, J. G. Gray, G. L. Grigg, A. C. Jain, K. N. Khanna, M. L. Rajakaruna, V. Rasanayakam, G. E. Rousseaux (Otolaryngology), E. J. Williams, J. A. Adams, S. D. Chatterjee (Ophthalmology), M. H. Cox, J. C. M. Currie, E. J. England, A. P. Fuller (Otolaryngology), B. E. Hagan, A. H. T. Hodgkinson, R. A. Howett, I. Kaplan, B. H. Kelham (Otolaryngology), H. M. Learoyd, C. V. Mann, J. A. P. Marston, V. G. Mavalankar, J. Moran, D. C. Patel, G. C. Robin, I. B. Tait, L. J. Walker, J. H. Williams, R. Attard, D. Churchill-Davidson, J. A. Girling, P. B. Humphris, S. R. Mitra, S. K. Nair, B. T. O'Connor, K. C. Perry, W. D. Proudman, G. R. A. Raad (Ophthalmology), M. P. Robinson, J. F. Sander, L. Souvlis, H. H. Srinivasan, P. Virmani, N. K. Yong, L. Das, I. D. A. Johnston, M. Y. D. Koawavwala, M. G. Maguire, B. A. Maurice, D. C. O'Sullivan, C. G. Paull, J. G. Ross, S. B. Singh, J. R. Solomon, D. E. Cam, R. D. P. Craig, A. R. Desai, K. H. Langford, M. B. Menelaus, R. P. Silverton, R. G. Smith, J. L. Dawson, H. F. Jeejeebhoy.

Faculty of Anaesthetists.—Dr. G. S. W. ORGANE, of the Westminster Hospital, has been elected dean, and Professor E. A. PASK, of King's College Medical School, Durham University, vice-dean of the Faculty for the coming year.

British Association of Urological Surgeons.—The 14th annual meeting, held in London from June 19 to 21, under the presidency of Mr. ARTHUR JACOBS, was attended by about 170 members. There was a full scientific programme, the main discussion being on carcinoma of the prostate. The papers will be published in the *British Journal of Urology*. The following were elected officers and members of council for 1958–9:

President, Mr. Arthur Jacobs; *immediate past president*, Mr. R. H. O. B. Robinson; *vice-president*, Mr. Hugh Donovan; *hon. treasurer*, Professor Victor W. Dix; *hon. secretary*, Mr. J. D. Fergusson; *hon. editorial secretary*, Mr. N. M. Matheson; *members of council*, Mr. F. R. Kilpatrick, Mr. W. S. Mack, Mr. T. J. Millin, Mr. R. A. Mogg, Mr. D. S. Poole-Wilson, Mr. N. L. Shepperd, Mr. J. Swinney, Mr. D. Innes Williams, and *(ex officio)* the president of the Section of Urology of the Royal Society of Medicine and the chairman of the editorial committee of the *British Journal of Urology*.

Liverpool University.—Dr. K. MCCARTHY and Dr. K. R. DUMBELL have been appointed senior lecturers in bacteriology; Dr. J. L. BRAITHWAITE and Dr. E. W. MACMILLAN senior lecturers in anatomy; and Dr. J. GLOVER, Ph.D., and Dr. H. K. KING, Ph.D., senior lecturers in biochemistry. These appointments take effect from next October.

Parapsychiatry and Human Development.—Messrs. S. Karger, of Basle, announce the publication of two new journals. *Confinia Psychiatrica*, whose editors are Drs. H. HEIMANN and T. SPOERRI, of Berne, is intended for papers on borderland subjects to psychiatry—psychology, behaviour research, endocrinology, pharmacology, sociology, medical history, etc. *Vita Humana*, edited by Professor H. THOMAE, of Erlangen, will be concerned with the science of human development and will cover such fields as anthropology, psychology, physiology, paediatrics, geriatrics, social hygiene, etc. Both journals are international in scope and will publish papers in English, French, or German, with summaries in all three languages; both are to appear quarterly, at an annual subscription in each case of 38.50 Swiss francs.

Health Service Supplement.—Next Monday (July 7) *The Times* will contain a 16-page supplement on the

National Health Service. The opening articles will discuss the general practitioner, the consultant service, local authority administration, and the cost of the Service. Other subjects include the future of private practice, hospital insurance, and the pharmaceutical industry.

"Family Doctor."—The July issue includes articles on suicide (Dr. E. H. HARE), Parkinsonism (Dr. DOREEN MOORHOUSE), and weight-lifting and "body-building" (by Mr. I. MACQUEEN, F.R.C.S.), as well as regular features such as "*Family Doctor* answers," the question-and-answer section for the layman.

COMING EVENTS

British Association of Paediatric Surgeons.—Annual meeting, July 23–25, in London. Details from Mr. R. ZACHARY, hon. secretary of the association, Children's Hospital, Sheffield, 10.

Prophylactic Medicine and Social Hygiene.—World congress at Gmunden, Austria, September 8–13. Details from the general secretariat, 41, Piaristengasse, Vienna, 8.

International Congress of Balneology.—Arranged by the Czechoslovak Society of Physiotherapy, September 8–13 at Marienbad. Details from the secretary of the congress, 5, Reznicka, Prague, 2.

International Collegium for Neuro-Psychopharmacology.—First international symposium, September 9–12, in Rome. Details from Dr. P. B. BRADLEY, Department of Experimental Psychiatry, the Medical School, Birmingham, 15.

International Scientific Film Association.—Twelfth congress in Moscow, September 10–20. Details about the British delegation and entries for the congress may be obtained from the Scientific Film Association, 164, Shaftesbury Avenue, London, W.C.2.

Institute of Medical Laboratory Technology.—Triennial conference, September 13–20 at Bristol University. Further details from the institute, 9, Harley Street, London, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Sunday, July 6

UNIVERSITY COLLEGE HOSPITAL, London.—10.15 a.m., clinical demonstration by Dr. H. A. Burt: Backache, its Prevention and Treatment. Open to all general practitioners.

Monday, July 7

LONDON UNIVERSITY.—At Wright-Fleming Institute Lecture Theatre, St. Mary's Hospital Medical School, 5 p.m., special university lecture in medicine by Professor Gerrit Bras (West Indies): Veno-occlusive Disease of the Liver.

Tuesday, July 8

INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. David Gitlin (Harvard Medical School): Plasma Protein Metabolism in the Nephrotic Syndrome.

INSTITUTE OF PSYCHIATRY.—5 p.m., public lecture by Professor George Rosen (Columbia University): Social Stress and Mental Diseases in the 18th, 19th, and 20th Centuries.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Bertram Louis Abrahams Lecture by Sir Lindor Brown, F.R.S.: The Mode of Action of Sympathetic Nerves.

Wednesday, July 9

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. G. Belyavin: Serology of the Influenza Viruses.

Thursday, July 10

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., F. E. Williams Lecture by Professor P. B. Medawar, F.R.S.: The Biology of Ageing.

ROYAL SOCIETY OF HEALTH.—At Town Hall, Lancaster, 10.15 a.m., Dr. R. W. Farquhar: Care of the Aged—Some Socio-medical Problems; Mr. F. Shaw: Public Control of Housing—A Broad Survey.

Friday, July 11

NUTRITION SOCIETY.—At Queen Elizabeth College, Campden Hill Road, London, W., Symposium on Applied Nutrition: The Human Factor in Group Feeding. Speakers, Mr. F. Le Gros Clark, Alexis Soyer (1809-1858)—Historical Note on His Contributions in Applied Nutrition; Sir Zachary Cope, The Medical Aspect of Soyer's Illness and His Crimean Experiences; Miss B. R. Stanton, The Human Factor in Hospital Feeding; Dr. J. J. O'Dwyer, Some Experiences in Group Nutrition; Brigadier J. A. Mullington, Human Problems in Feeding Service Men; Miss P. Roscoe, The Problems of Feeding Women in Industry; Miss F. E. Morkam, The Human Factor in School Dinners; Mrs. D. W. Newman, Appetites in Retirement: The Organized Feeding of Old People.

Saturday, July 12

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Royal Manchester Sick Children's Hospital, 2 p.m., meeting.

APPOINTMENTS

CLYNICK, F. E., M.B., Ch.B., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist, St. Peter's, St. Paul's, and St. Philip's Hospitals, London.

FLOOD, CHARLES, M.D., M.R.C.O.G., Honorary Assistant Obstetrician and Gynaecologist, Hospital of St. John and St. Elizabeth, 60, Grove End Road, London, N.W.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Thérèse M. Vanier, M.B., B.Chir., House-physician; K. J. Brown, M.S., F.R.A.C.S., House-surgeon to Orthopaedic and Plastic Departments; P. J. Koblenzer, M.B., B.S., Assistant Medical Registrar; C. G. H. Newman, M.B., B.S., M.R.C.P., D.C.H, House-physician; R. H. R. White, M.B., B.Chir., M.R.C.P., D.C.H., Medical Registrar and Pathologist; Rosalie E. B. Eastwood, M.B., Ch.B., Resident Officer to Department of Neurology and Neurosurgery; Dinah C. M. Henderson, M.B., Ch.B., D.M.R.D., Senior Registrar in Radiology (to be shared with Royal Free Hospital); D. Barltrop, M.B., B.S., and G. W. Hatcher, M.B., B.S., D.Obst.R.C.O.G., House-physicians; J. M. Kingsmill Moore, M.B., B.Ch., and J. Abrahamson, M.B., Ch.B., House-surgeons; D. A. Larnder, M.B., Ch.B., F.R.C.S., and C. J. Stevenson, M.D., M.R.C.P., Senior Registrars to Department of Dermatology; R. M. Ingram, B.M., B.Ch., Senior Registrar to Ophthalmic Department; D. G. Mackie, M.B., B.S., Resident Ear, Nose, and Throat Registrar; June E. Brett, M.B., B.Chir., F.F.A. R.C.S., D.A., Junior Anaesthetic Registrar.

LONDON COUNTY COUNCIL.—The following have been appointed whole-time medical officers in the Council's Public Health Department: T. J. Mahon, M.B., B.Ch., L.M., D.P.H., D.C.H., C.P.H., R. W. Watton, M.B., B.S., D.P.H., W. T. Orton, M.B., B.Ch., D.P.H., and M. L. Graeme, M.B., B.Chir., D.P.H.

MANCHESTER REGIONAL HOSPITAL BOARD.—N. S. Gordon, M.D., M.R.C.P., M.R.C.P.Ed., Consultant Neurologist, Booth Hall Hospital, Manchester, Royal Manchester Children's Hospital, with additional duties at David Lewis Epileptic Colony, Cheshire, and in Preston Hospital Centre; E. Sherrah-Davies, M.B., B.Chir., F.R.C.S., D.M.R.T., Consultant Radiotherapist, and K. E. Halnan, M.D., F.F.R., D.M.R.T., Assistant Radiotherapist (S.H.M.O.), Christie Hospital and Holt Radium Institute, Manchester; G. R. Carr, M.D., Ch.M., F.R.C.S., Consultant Surgeon, Stockport and Buxton Group of Hospitals; D. L. Chadwick, M.D., F.R.C.S., D.L.O., Consultant Ear, Nose, and Throat Surgeon, Crumpsall, Ancoats, and Manchester Ear Hospitals.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—Ella Preiskel, M.B., B.S., D.M.R., Consultant Radiologist, Willesden General Hospital; S. A. James, M.R.C.S., L.R.C.P., D.Phys.Med., Assistant Physician in Physical Medicine (S.H.M.O.), West Herts Group; Susan Gordfarb, M.D., Assistant Pathologist (S.H.M.O.), Clare Hall Hospital; F. J. Fowler, M.B., Ch.B., Senior Administrative Medical Officer, as from August 1, 1958; D. Preiskel, M.D., M.R.C.P., Consultant Physician in Physical Medicine, Acton Hospital; J. L. Anderson, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist, Edgware General Hospital; W. C. Robinson, F.R.C.S.Ed., Consultant Orthopaedic Surgeon, and T. Faulkner, F.R.C.S., Consultant Plastic Surgeon, St. Charles' Hospital; G. F. Swann, M.B., B.S., M.R.C.P., D.M.R.D., Consultant Radiologist, West End Hospital for Neurology and Neurosurgery; K. E. Schmidt, M.D., D.P.M., Assistant Psychiatrist (S.H.M.O.), Hill End Hospital; G. Stroh, M.B., B.S., D.P.M., Consultant Psychiatrist in Charge, High Wick, Tyttenhanger, St. Albans; Edwina R. Goodall, M.B., B.S., D.M.R.D., Consultant Radiologist, Ashford and Hounslow Hospitals; J. G. Roberts, M.B., Ch.B., F.R.C.S., Consultant Assistant Neurosurgeon, Central Middlesex Hospital; G. E. Stein, M.B., B.Chir., F.R.C.S., Consultant Ear, Nose, and Throat Surgeon, Acton Hospital; Mary I. Wray, M.B., B.S., D.M.R.D., Consultant Radiologist, Barnet General Hospital; J. R. E. Richardson, M.R.C.S., L.R.C.P., Assistant Pathologist (S.H.M.O.), King Edward Memorial Hospital, Ealing.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—P. F. Boreham, M.Chir., F.R.C.S., Consultant General Surgeon in North Gloucestershire Clinical Area; P. A. Skinner, M.B., B.S., F.F.A. R.C.S., Senior Anaesthetic Registrar at Frenchay Hospital, Bristol; J. L. James, M.B., Ch.B., Medical Registrar in Bath Group of Hospitals; H. A. McClelland, M.B., B.S., D.Obst.R.C.O.G., D.C.H., Medical Registrar at Cheltenham General Hospital.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Champion.—On June 21, 1958, at "Lawnswood," Ventnor, Isle of Wight, to Valerie, wife of Dr. Alan Champion, a daughter—Rosemary Ann.

Dixey.—On June 22, 1958, at Newmarket General Hospital, to Christie (formerly Humphrey), wife of Dr. John Dixey, of Isleham, Cambs, a son and a daughter.

Harman.—On June 2, 1958, at Grey's Hospital, Pietermaritzburg, South Africa, to Dr. and Mrs. M. J. Harman, twin sons.

Merriweather.—On June 19, 1958, at Lobatsi Hospital, Bechuanaland, to Dr. and Mrs. A. M. Merriweather, a daughter—Winifred Joy.

Reynolds.—On June 25, 1958, at Brighton General Hospital, to Patricia (formerly Aldridge), wife of Patrick C. Reynolds, a daughter—Christine Anne.

DEATHS

Ashton.—On June 10, 1958, Joseph Ashton, M.B., of Colwyn Bay, Denb., formerly of Wandsworth, London, S.W., aged 88.

Bryson.—On June 7, 1958, at St. Leonards-on-Sea, Sussex, Alexander Carruthers Bryson, M.B., B.S., formerly of Shanghai, China.

Cosgrave.—On June 20, 1958, Alexander Kirkpatrick Cosgrave, *M.C.*, V.D., M.B., B.Ch., D.P.H., D.T.M.&H., of Westerleigh, Beaconsfield, Bucks, late of Malaya.

Garlick.—On June 6, 1958, at Lucerne, Switzerland, George Herbert Garlick, M.R.C.S., L.R.C.P., D.M.R.E., of Singapore.

Innes.—On May 27, 1958, at Menton, France, Arthur Innes, M.B., Ch.B., F.R.F.P.S., of Greenways, South Lynn Drive, Eastbourne, Sussex, late of Glasgow.

Melvin.—On June 20, 1958, at Sherwood, Lofthouse, near Wakefield, Yorks, Moray Melvin, M.D., aged 62.

Pereira.—On June 11, 1958, at his home, Bexley, Kent, Henry Manning Pereira, L.R.C.P.&S.Ed., L.R.F.P.S., D.P.H., late of Homerton, London, E., aged 87.

Wilson.—On June 10, 1958, Thomas Robert Wilson, L.R.C.P.&S.Ed., L.R.F.P.S., of Skegness, Lincs, formerly of Wainfleet, Lincs.

Yates.—On April 17, 1958, Robert Burton Meikle Yates, M.B., Ch.B., of Market Drayton, Salop.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Origin and Spread of Influenza

Q.—*Does the natural history of influenza epidemics and pandemics give any indication of their usual place of origin and rate of travel?*

A.—The short answer to this question is no. The precise origin of the recent Asian epidemic is unknown, though it is said to have appeared first in a relatively small area of south-west China. The 1949 European epidemic broke out among shepherds in Sardinia. The first cases of the 1918 pandemic are said to have occurred in Army camps in the U.S.A., and the outbreak in Europe occurred after the arrival of American troops in France. The 1889 pandemic has been traced to north-central Asia. Thus it cannot be said that there is any usual place of origin for influenza epidemics nor that the first sufferers are people with an exceptional susceptibility to the virus. But the age-specific attack rate of the recent epidemic was highest in children. Adults who were in close contact with children probably suffered more severely than those with less intimate contact. This was shown by a change in the age-distribution of deaths as the epidemic progressed. There was a shift in the distribution towards the older age-groups of the population in successive weeks of the epidemic, thus suggesting a gradual involvement of the more resistant members of the population. The rate of travel of the Asian epidemic appears to have been no greater than that of the epidemics of 1890 or 1918. It was noteworthy that local outbreaks followed the arrival of ships rather than aircraft, and this suggests that a sufficient quantum of infection must be imported before spread takes place.

Potassium Bircarbonate and Chlorothiazide

Q.—*Is it possible to give potassium bicarbonate instead of potassium chloride to counteract hypokalaemia in chlorothiazide therapy?*

A.—One of the practical reasons against giving potassium bicarbonate is that it is not possible to make it into tablets. There is, however, 1 g. of potassium bicarbonate in 14 ml. of mist. pot. cit. et hyoscyami, so it would theoretically be possible to give enough, although this is a most unpleasant mixture to take. The main disadvantage is that it is an alkali. Chlorothiazide acts chiefly on chloride excretion, and therefore potassium chloride might be expected to be beneficial in this respect. Potassium bicarbonate, on the other hand, will enhance the alkalaemia which chlorothiazide tends to produce by virtue of its action as a carbonic-anhydrase inhibitor.

Recurrent Sprains

Q.—*What can be done to prevent recurrent sprains of the ankle in a woman which occur on the slightest provocation since an original sprain 25 years ago?*

A.—When a woman suffers recurrent sprains of the ankle after an original "sprain" 25 years ago it may well be that the original injury was in fact something more serious than a simple sprain. She may possibly have sustained a complete rupture of the lateral or deltoid ligaments of the ankle. She may even have fractured or avulsed the tip of the medial or lateral malleolus. Such lesions could have been overlooked at the time and the injured ankle treated as an uncomplicated sprain by strapping only.

Often these more serious injuries can be detected with certainty only by radiography with the foot passively held in forced full inversion and eversion. Disruption of the ankle-joint on its lateral or medial aspect will then be shown by the opening up of the talo-tibio-fibular mortise on the respective side.[1] This kind of lesion usually demands more radical surgical measures than simple strapping support. Failure correctly to diagnose the full extent of the injury and to give proper initial treatment results in a permanently unstable ankle-joint. In view of this possibility in the patient in question, she should be referred to a consultant orthopaedic surgeon for any surgical treatment that might be necessary.

Apart from the more serious causes suggested, recurrent ankle sprains in women are frequently due to a combination of obesity, unsuitable footwear, and weak calf muscles. The treatment of these is diet, low-heeled, lace-up shoes, and supervised ankle exercises in a physiotherapy department.

REFERENCE

1 Watson-Jones, R., *Fractures and Joint Injuries*, 1955, 4th ed., volume 2, p. 817. Livingstone, Edinburgh.

Nasal Haemolytic Streptococci

Q.—*Why is it that when haemolytic streptococci are found in a throat swab they are not usually found in a nasal swab taken at the same time?*

A.—The area sampled by an anterior nasal swab is remote from the fauces and has a different flora. The direction of flow of secretion produced by the action of the nasal ciliated epithelium is from before backwards, and this is an obstacle to the migration of throat bacteria even into the posterior part of the nasal cavity.

Haemolytic streptococci are cultivated from throat swabs in patients who have an acute streptococcal tonsillitis or a more diffuse form of angina, or from those who are tonsillar carriers of this organism. Unless there is an accompanying rhinitis, which is sometimes seen in both the acute and the chronic infection, there is no reason why the organism should also be found in the nose.

Infection from Books

Q.—*Can library books convey infection? What measures are suitable for disinfecting them?*

A.—Pathogenic organisms such as haemolytic streptococci can certainly be recovered from books, but it is difficult to prove that infection has been caused by them. It is highly likely that when the organism is very resistant to light and drying, as in smallpox, books could be dangerously infectious. Infection with various diseases has often occurred when human contact with another case could be excluded. Laundry articles are then the commonest vehicles of infection, but, allowing for the difference in the amount of contact and handling, books could act in the same way. It is important to remember that it is an offence under the Public Health Act to allow a book from a public or circulating library to be used by a person suffering from a notifiable disease: if it has been so used, the local authority must disinfect or destroy the book. Unless the book is valuable, the safest measure is to burn it. For disinfection, books should be exposed in a special chamber to a maximum concentration of formaldehyde for at least 24 hours. The gas has limited powers of penetration, so that the books should be hung on wires in such a way that the pages are kept as open as possible.

Fats and Coronary Disease

Q.—*What is the strength of the evidence of a relationship between dietary saturated fatty acids and coronary artery disease?*

A.—Epidemiological studies indicate that in countries and communities where the total fat consumption is high the incidence of coronary artery disease is also high. Unfortunately very little is known about the contribution of saturated or of unsaturated fatty acids to the total fat intake in various countries, and so it is impossible at present to relate the incidence of coronary disease to excess or lack of any particular type of fatty acid. Most of us in this country

eat more or less the same amount of fat, but fortunately most of us do not develop myocardial infarction or even advanced coronary atherosclerosis. It is obvious, therefore, that the total intake of fat is only one part of the aetiological picture of coronary disease.

All that can be said at present is that saturated fatty acids elevate the serum cholesterol and that the serum cholesterol is often elevated in patients with coronary disease. These two observations may not be very closely related, and so far there is no evidence that there are more saturated or less unsaturated fatty acids in the serum of patients with coronary disease than in healthy controls. Thus, the evidence for a relationship between saturated fatty acids and coronary artery disease is no more than circumstantial.

Hard Beds for Small Children

Q.—*Is a hard bed without pillows satisfactory for small children?*

A.—Sleeping on a hard bed without pillows is a perfectly satisfactory orthopaedic state for normal young children. It is important that the bed should not sag in the middle. A bed or mattress may be hard yet still sag because the bedstead springing is of poor design. In this respect a fine wire mesh over vertically placed coiled springs is a better base than a wire mesh with no supporting vertical springs.

On top of a sprung base should be a firm mattress, not a spring interior or foam rubber one. An interior sprung or foam rubber mattress on a sprung base is an unhealthy combination, as it is too soft, sags too easily, and predisposes to low back pain. It can be improved by placing wooden boards or a large sheet of thick plywood between the mattress and the bedstead. A very satisfactory, and inexpensive, bed for two young children is to make wooden bunks in which are placed 4-in.-thick (10-cm.) foam rubber mattresses resting on a plain wooden board base. As there is only board and no springing under the mattresses the latter are compressed evenly by the body weight and do not sag.

Pillows are not essential for normal children provided they sleep well without them. Pillows assume more importance if a child has some deformity like torticollis or scoliosis. For the normal child a single pillow is best. If there is any allergic tendency a pillow filled with soft latex rubber foam (in one piece or foam rubber chips) should be chosen in preference to a feather or kapok pillow.

NOTES AND COMMENTS

Thin and Greasy Hair.—Dr. E. J. MOYNAHAN (London, S.E.1) writes: It is a popular belief, evidently shared by your expert ("Any Questions?" June 7, p. 1365), that massage of the scalp will "delay the progress of hair loss" in a young man with premature baldness. This is a condition which is determined genetically and invariably inherited as a dominant character. The gene responsible for it, like the gene (or genes) which give rise to a number of other traits affecting the skin, such as hirsutism in the female, acne vulgaris, psoriasis, and loss of the so-called juvenile hair-line on the forehead during adolescence, is much more frequent in white populations than in those of other races. There is little evidence which supports the view that any form of treatment, other than castration (which is rather a high price to pay to preserve one's locks), will arrest or slow up the process of hair loss in common baldness, whether premature or not. There is evidence, however, that scalp massage may, in fact, make the baldness worse. It is not surprising that this is so, since it is a common experience to find that many of the follicles which are ultimately destined to lose the power of producing hair first show this by producing thinner and shorter hairs before giving up hair-production altogether. These hairs, which are more fragile than the normal terminal scalp hair, are apt to break off when the scalp is massaged, thus making matters worse for the balding individual. The evidence that any improvement in the local circulation consequent on massage of the scalp will help such an individual to retain his hair is even more slender, and must be regarded as pure speculation for as long as we remain as ignorant as we do of the factors which are responsible for the progressive atrophy and/or disappearance of the hair follicles. A great deal remains to be done, by way of investigation of the normal cycle of hair growth in the human scalp, before any useful suggestions can be made to help those who are so genetically endowed to postpone or avoid their fate.

OUR EXPERT replies: The fact that premature baldness depends partly upon genetic factors does not in itself mean that it cannot be influenced by treatment. The same argument could apply to psoriasis and acne, which Dr. Moynahan also mentions. The value of massage or of any kind of treatment is extremely difficult to assess in a disorder, such as this, which runs a variable and unpredictable course. It is, however, a widely held belief among doctors as well as the lay public that massage has some beneficial effect in these cases. It is for this reason that I said no more than that it may be possible to delay hair loss. Most patients certainly prefer to do something rather than wait for the inevitable progress of their baldness. The harmful effect of massage on the hair results from friction between the fingers, the hair, and the scalp. This point has been well brought out by the observations of Bowers.[1] Massage with the flat of the hand is recommended as free from this risk.[2] As Dr. Moynahan points out, a great deal remains to be known about the mechanism of hair growth, but until knowledge is more precise we should not be too ready to condemn empirical treatment.

REFERENCES

1 Bowers, R. E., *Brit. J. Derm.*, 1950, **62**, 262.
2 Sidi, E., and Aron-Brunetière, R., *Précis de Dermatologie Corrective*, 1952. Paris.

Senna and Colic.—Mr. E. W. GODDING (Westminster Laboratories Ltd., London, N.W.1) writes: Your expert ("Any Questions?" May 31, p. 1313), in quoting Professor Duncan's[1] findings of a 17% incidence of griping in puerperal women following relatively large doses of standardized senna, omitted reference to a much more practical aspect of Professor Duncan's data. Thus, in the same article he states: "The fact that a higher proportion of the "senokot" series had gripes is thought to be due to overdosage, because for the purpose of the trial it was necessary to give the same dose to all patients. Further experience with senokot has shown that an occasional patient experiences severe gripes in spite of smaller dosage, *but this has been so infrequent* [my italics] that it has not detracted from the advantages of the drug."[2] The clinical reports which have reached us during the past five years leave little doubt as to the correctness of the statement[2]: "The great advantage of prescribing a standardized preparation of constant laxative action is that, once the dose for each patient is decided, there should be no griping, since this seems to be a symptom of overdosage."

REFERENCES

1 Duncan, A. S., *Brit. med. J.*, 1957, **2**, 439.
2 *Lancet*, 1952, **1**, 655.

Correction.—In the answer to the question on diuretics ("Any Questions?" May 31, p. 1313), mercaptopurine was listed as a mercurial diuretic. The name of the drug should have been mercaptomerin.

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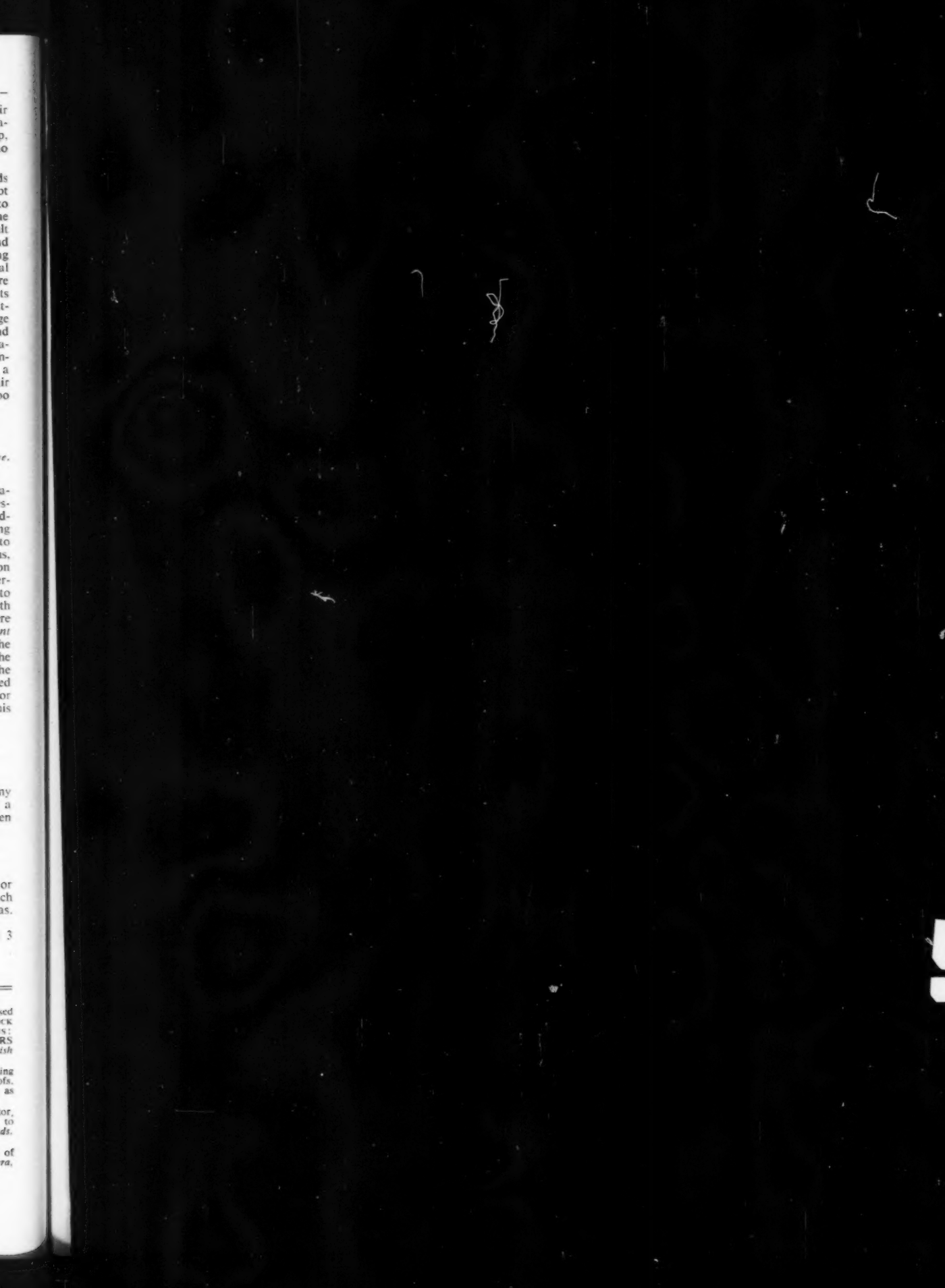
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